# Atypical femoral shaft fractures (AFF) in NHS Grampian: incidence, underlying associations and assessment of DXA scanner software designed for early identification of AFF.

Submitted by Diane Smith to the University of Exeter

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I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or any other University.

Signature: ……..

**Abstract**

Objectives: The objectives of this study were to assess the clinical utility of extended femur DXA scan software in the identification of incomplete atypical femoral fractures in a routine clinical population; to assess the short term in-vivo precision of extended femur scans; and to investigate of the incidence of atypical femoral fractures between 2008 – 2018 within NHS Grampian, to provide a context for DXA scan findings.

Method: A short term precision study was undertaken using the GE Lunar extended femur DXA scanning software, with 30 participants exposed to duplicate extended femur scans. From this, analysis was undertaken to assess and compare beaking index measurements and bone mineral density measurements from the software.

Audits of scan acquisition, assessment and software stability were undertaken in order to assess the scan software and staff compliance with training, the service was routinely scanning the extended femur in all patients over 20 years of age. The images acquired were used to assess the utility of the software in identifying and measuring the endosteal femoral cortex, in contrast to the visual assessment of the same areas by experienced members of staff.

A retrospective review of patients within NHS Grampian identified as having femoral fractures over a ten year period was carried out in order to identify the incidence of those suffering atypical femoral fractures within this healthcare service.

Results: The visual assessment of the femoral cortex was found to be more effective and efficient than the scan software alone in identifying abnormalities, in line with the findings of previous studies comparing automated analysis with visual assessment. There was no identified difference in bone mineral density precision errors at the hip precision using the extended femur scanning software compared to standard hip measurements in the 30 patients included in the study, but there were some discrepancies in duplicated beaking index measurements in part thought to be caused by slight differences in positioning for scans. Least significant change was measured as 5.68% at femoral neck and 3.96% for total hip across the study, well within the parameters of ISCD accepted figures of 6.9% for femoral neck measurements and 5% for total hip.

A negative predictive value of 100% was found when using the software in a clinical setting for six months, with a positive predictive value of 0.01% and an accuracy rate of 82.07%. Around 20% of patients scanned were found to have peaks ≥1mm on extended femur DXA scan automated analysis, however these were found to have an entirely normal appearance on visual inspection of images acquired. Audits of scan positioning, analysis and assessment of extended femur scans identified several positioning anomalies which were addressed when identified.

Of the 7102 patients reviewed with femoral fractures over a period of ten years, 13 (0.18%) were identified as suffering atypical femoral fracture, with one of those patients having bilateral AFF. All the patients suffering AFF were also found to have varying lengths of bisphosphonate exposure.

Discussion: Measurement of bone mineral density (BMD) by DXA is routinely used to diagnose osteoporosis and monitor treatment response. When comparing scans it is important to distinguish between real changes in BMD as opposed to changes related to the measurement process itself i.e. the precision of measurements. There is no published evidence of this type of beaking index precision study having been undertaken, indeed studies performed on extended femur scanning have all utilised slightly different methodology, making direct comparison impossible.

Atypical femoral fracture is a rare but recognised complication of osteoporosis treatment and the use of extended femur scan software demonstrates a promising ability to identify and assess incomplete AFF in conjunction with routine bone mineral density measurement, identifying abnormal thickening or peaks in the lateral femoral cortex aided by automated software measurements of beaking index. However, in light of the study findings, visual assessment of the femoral cortex must also be undertaken by the operator to ensure false positives are eliminated from further investigation. It would be highly unlikely in the context of current literature that 20% of a general population would exhibit signs of iAFF on extended femur scanning.

Conclusion:

The extended femur scan acquisition and automated analysis was found to expose the patient population to a slightly higher radiation exposure. The automated analysis was not acceptable as a stand alone assessment of the femoral cortex, visual assessment was essential in tandem to ensure software anomalies were not reported as suspicious peaks, the investigation of which

would place pressures on imaging services and also un-necessary anxiety to patients.

Patient positioning as per the GE Lunar scan handbook is highlighted as important in terms of reproducibility of scans and also for accurately measuring the femoral cortex. For patients and clinicians there is reassurance that although such abnormalities are rare, affecting 0.18% of the local population, abnormalities will be identified by the software and highlighted by the reporting clinician, allowing monitoring and intervention as appropriate.

Acknowledgements

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List of abbreviations

ADT – Androgen Deprivation Therapy

AFF – Atypical femoral fractures

AI – Aromatase Inhibitor

AIDS – Acquired Immunodeficiency Syndrome

ANOVA –Analysis of variance

ASBMR – American Society for Bone and Mineral Research

ASIS – Anterior superior iliac spine

BI – Beaking index

BMD - Bone mineral density

BMI – Body mass index

CD – Coeliac disease

CHI – Community Health Index

CI – Confidence interval

COVID 19 – Coronavirus

CT – Computed Tomography

CV – Coefficient of variation

DXA – Dual-Energy X-ray Absorptiometry

FRAX – Fracture Risk Assessment Tool

GC – Glucocorticoid

GE – General Electric

HCPC – Health and Care Professions Council

HIV – Human Immunodeficiency Virus

HRT – Hormone Replacement Therapy

iAFF – Incomplete atypical femoral fracture

ICD – International Classification of Diseases

IM - Intramedullary

IRAS – Integrated Research Application System

ISCD – International Society of Clinical Densitometry

LSC – Least significant change

MRI – Magnetic Resonance Imaging

NICE – National Institute for Health and Care Excellence

NHS – National Health Service

NOGG – National Osteoporosis Guideline Group

NOS – National Osteoporosis Society

NPV – Negative predictive value

NSAID – Non-Steroidal Anti Inflammatory Drugs

ONJ – Osteonecrosis of the jaw

PA – Posterioantrerior

PACS – Picture Archiving and Communication System

PPI – Proton Pump Inhibitor

PPV – Positive predictive value

RA – Rheumatoid arthritis

RANK – Receptor activator of nuclear factor $^{k}$ B

RANK L – Receptor activator of nuclear factor $^{k}$ B - ligand

RMS – Root mean square

ROI – Region of interest

ROS - Royal Osteoporosis Society

SD – Standard deviation

SIGN – Scottish Intercollegiate Guidelines Network

SOP – Standard operating procedure

SSRI – Selective Serotonin Reuptake Inhibitor

T1DM – Type 1 (insulin dependent) Diabetes Mellitus

T2DM – Type 2 Diabetes Mellitus

UK – United Kingdom

VDR – Vitamin D receptor

WHO – World Health Organisation

An abstract from this thesis on the in-vivo precision study has been accepted by the Royal Osteoporosis Society to present at the 2020 conference (postponed).

# 1 Introduction.

This section presents an overview of osteoporosis, the use of DXA scanning in the diagnosis, monitoring and management of the condition and the use of new extended femur DXA scanning software.

## 1.1 Motivation for the study.

Atypical femoral fractures (AFFs) have been associated with the long term use of bisphosphonate drugs used to treat osteoporosis and were first described in the seminal paper as being atraumatic and occurring in the presence of long term Alendronate therapy [1]. Numerous subsequent studies have demonstrated similar findings, highlighting the significant morbidity associated with these types of fractures [2-5]. However, prior to complete fractures, there are often warning signs. Patients may report persistent groin, thigh or hip pain and on imaging “beaking” can be visualised on the lateral aspect of the femur. These early features provide the potential for opportunistic screening for AFF using dual energy x-ray absorptiometry (DXA) as a low dose imaging technique where patients will be scanned routinely, as a means of monitoring their response to treatment and assessment for drug treatment holidays. Incomplete AFFs have been identified on imaging through thickening of the lateral femoral cortex, presenting as a peak, demonstrated in figure 1.1.

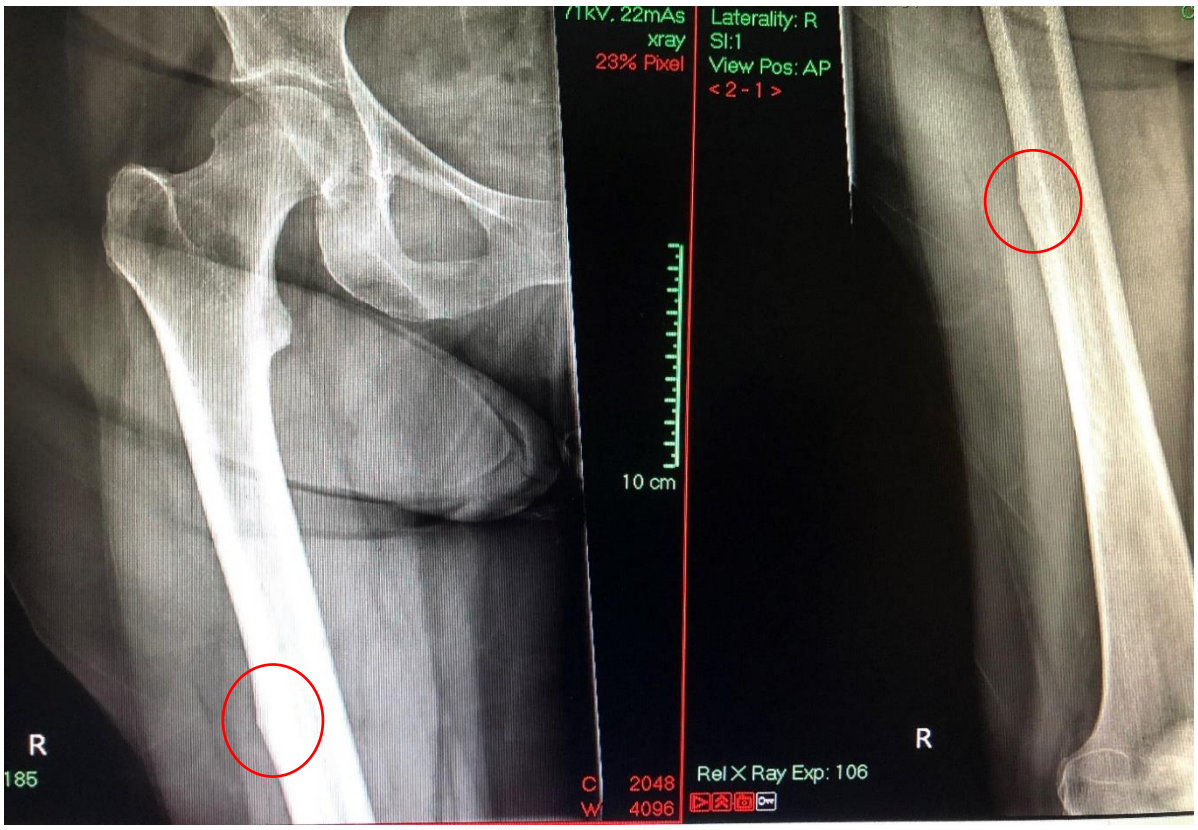



Figure 1.1 Radiographs of the right femur with lateral peak identified.

Dual-energy x-ray absorptiometry (DXA) is widely recognised as the gold-standard imaging modality for the measurement of bone mineral density (BMD) for the diagnosis, management and treatment response of osteoporosis medications [6].

New DXA scanning software has been developed by manufacturers General Electric (GE) Lunar, which is compatible with scanners and software already used in a clinical setting, presenting the ability to routinely scan and assess the full length of the femur and highlight cortical changes. The motivation for this study is the evaluation and assessment, in routine clinical use, of the extended femur scanning software developed by GE, designed to be used as part of routine DXA scanning, to identify changes in the femoral cortex in a clinical population.

## 1.2 Femur and bone biology.

This section outlines the structure of the femur, bone biology and the relevance of muscle insertion points with regard to DXA scanning and peaks seen on extended femur scans.

### 1.2.1 Bone biology and osteoporosis.

Bone is an active tissue within the body that is constantly remodelling in response to mechanical stresses and strains. Osteocytes, osteoclasts and osteoblasts all work together in the bone remodelling process, with osteocytes sending signals to osteoblasts and osteoclasts on the bone surface [7]. Micro-architectural defects within the bone structure lead to increased risk of fracture owing to increased fragility of the bone. Other factors influencing bone strength are the shape, size and mineralisation of the bones. A continuous process of bone remodelling occurs throughout life, with mature bone resorption closely coupled with new bone deposition and ossification, which maintains bone strength, density and integrity. When this process becomes imbalanced, through age, illness or medication, it leads to net loss of bone, degradation of bone microarchitecture, and ultimately a higher fracture risk, potentially leading to osteoporosis. These changes take place at a cellular level within the bone structure [7-10].

Bone formation occurs in five stages, as demonstrated in figure 1.2. In this cycle the stimulation and differentiation of preosteclasts to osteoclasts occurs, they then begin to digest mature bone cells. Following this, there is an end to

the resorption process and osteoblasts begin to create new bone, when cells rest on the bone surface [11].

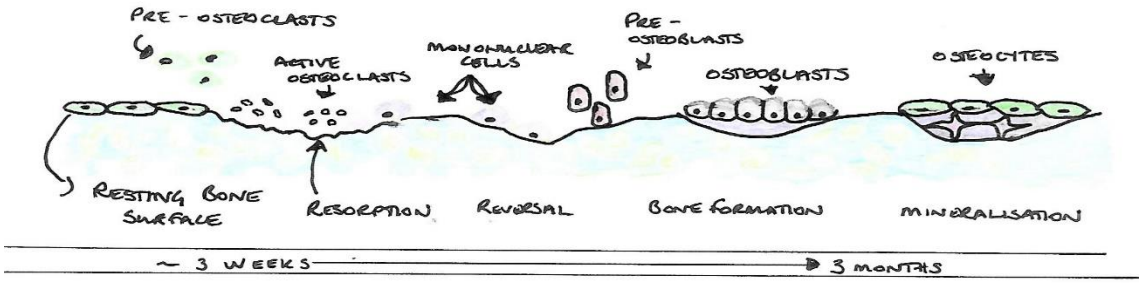



Figure 1.2 Bone remodelling process.

Osteoblasts, bone-forming cells that take charge of the bone turnover cycle, are found in the periosteum within the ossification centres of juvenile bone, the ends of diaphyseal bone and at the site of fractures. Osteoblasts produce and secrete bone matrix, primarily composed of calcium phosphate and collagen. This reaction is in response to mechanical stress and also to growth factors, which stimulate osteoblasts to form bone. Osteoblasts release high levels of alkaline phosphatase and osteocalcin, and the amounts of these proteins in circulation is a reflection of bone formation rates [7].

Osteoclasts, primarily responsible for the process of bone resorption, are essential for bone remodelling and changes in bone shaping of the mature skeleton. Osteoclasts work at the surface of the bones, attaching to osteons,

on an ongoing process of resorption, producing and excreting enzymes that dissolve bone. During this process, collagen is broken down to amino acids, calcium, magnesium and phosphate to be used elsewhere in the body [7, 8, 12].

Several hormones have been identified as having a major influence on bone turnover, namely oestrogen, testosterone, calcitonin and parathyroid hormones, with oestrogen thought to have the most direct influence on bone health and turnover. These hormones trigger a complex reaction within the bone cells, prompting increased activity within osteoblast cells, which affects the communication between osteoblasts and osteoclasts [10]. This has the effect of stimulating bone turnover. Both oestrogens and androgens inhibit osteoclast regeneration, with oestrogens inducing osteoclast apoptosis while, in contrast, glucocorticoids prolong the life span of osteoclasts [10, 13, 14]. The rapid decrease in oestrogen levels at menopause causes an equally rapid loss of trabecular bone in women, while in men the bone loss trajectory is much slower and steadier decline. A visual representation of bone density trajectory through life is displayed in figure 1.3 (adapted from Compston 2009).

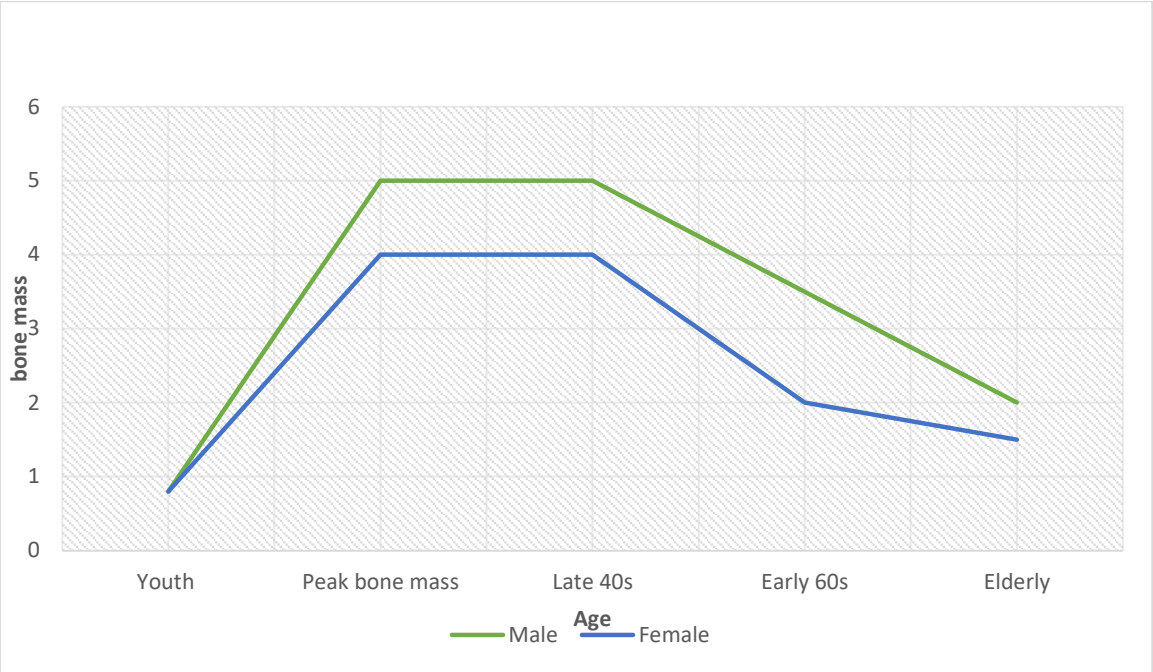



Figure 1.3 Bone density trajectory through life, split by sex (adapted from [10])

Osteocytes are mature osteoblastic cells which become trapped within newly laid down bone, evenly distributed within the bone matrix. Osteocytes are the most abundant and long living cells in the bone, becoming responsible for the maintenance and monitoring of bone tissue health. This is in response to cues both hormonal and mechanical, and is possible due to their location and numbers. Osteocytes are also responsible for the regulation of osteoclasts and osteoblasts, and detectors of microdamage within bone which has been induced by fatigue. Signals are sent to osteoclasts, whereby remodelling of the damaged bone is induced. Osteocytes also monitor and respond to changes in hormone circulation, adjusting rates of bone formation and resorption as necessary, as demonstrated in figure 1.2 [7, 8].

### 1.2.2 Structure of the femur.

The diaphysis, or shaft, of femur is composed of cortical bone. This type of bone is responsible for around 80% of the skeletal system and has great resistance to bending and torsion. In this type of bone, osteocytes and extracellular matrix are tightly packed and combine in a concentric fashion known as a Haversian system, or osteon. Central canals carry blood vessels, nerve fibres and connective tissues. The blood flow nourishes these bone cells via gaps between osteocytes. These canals extend longitudinally through the bone tissue, connected by Volkmann's canals running transversely. The transverse canals carry larger nerves and blood vessels, which the blood vessels and nerves in the smaller longitudinal canals use to connect with the surface of the bone [7, 8].

As the skeletal system ages, cortical bone becomes more porous, reducing in strength while gaining surface area. This is most relevant in the case of long bones such as the femur, where increased porosity near the periosteal surface causes a greater loss of strength. Cortical bone also supports bending at the distal end of the neck of femur [7-9].

### 1.2.3 Femoral muscle insertions and their influence on DXA scanning.

The femur is the insertion point for numerous muscles which facilitate movement of the hip and leg. A major muscle at the distal femur is the gluteus maximus, which has an insertion point within the pelvis and another on the gluteal tuberosity at the head of the linea aspera, a bony prominence running down the posterior aspect of the femur. The origins of the gluteus maximus can be visualised on an over-rotated DXA scan image and has the potential to lead

to false positive peaks when using extended femur scan software. One study found that prominent gluteus maximus insertion coupled with the over-rotation internally of the femur brings the linea aspera into relief against the lateral cortex of the femur, something which could be mistaken for an abnormality on DXA imaging. However, in this case, abnormality was ruled out using computed tomography (CT) imaging, where the positioning and location of the suspicious area was found to be posteriolateral rather than lateral and demonstrated the insertion of the gluteus maximus tendon to the femur at the linea aspera [15]. These abnormalities are labelled as tug lesions and have a smoother contour with no break in the periosteum, which is in contrast to true beaking [16]. Such peaks are identified at approximately 120 mm from the tip of the greater trochanter, as measured and identified automatically by the scan software, demonstrated in figure 1.4. Those that can be identified as beaking will have a lucent line in the centre of the peak, indicating micro fracture, and will generally be identified by DXA scanning software as a sharp peak on the beaking profile graph.

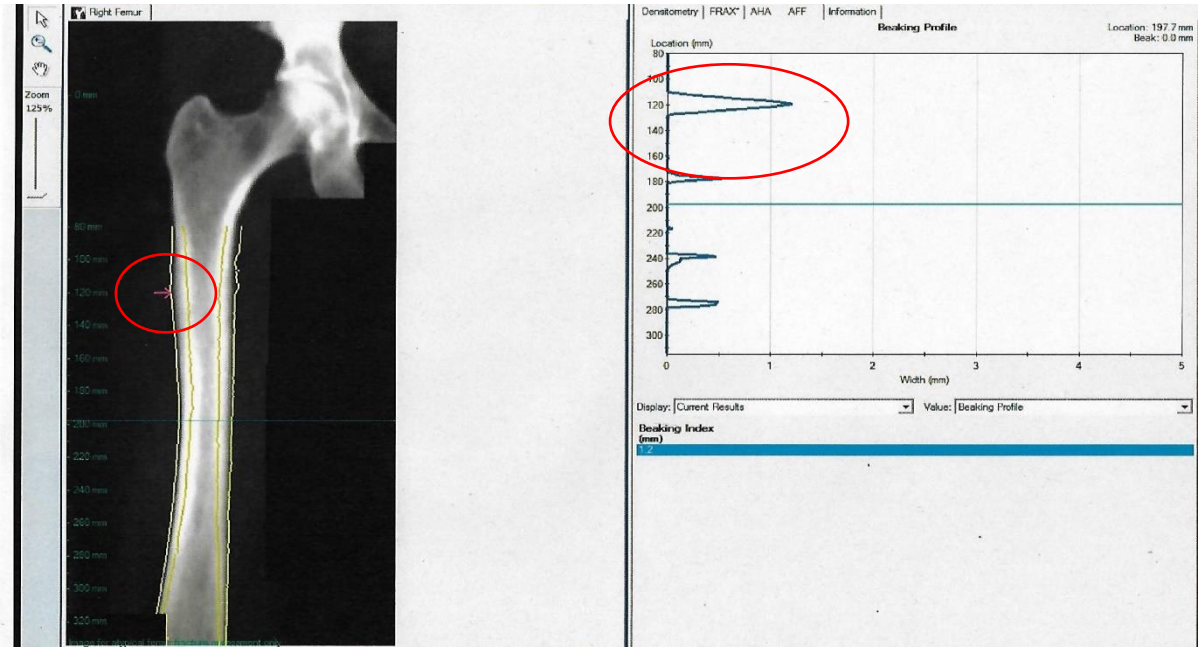



Figure 1.4 False positive beaking on an extended femur DXA scan, highlighting prominent gluteus insertion point.

## 1.3 Osteoporosis.

This section seeks to cover the definition of osteoporosis, the use of bone strengthening medication to treat osteoporosis and monitoring of the aforementioned therapy. An understanding of bone turnover and the effects of this with the use bone strengthening medication is essential to appreciate its benefits and balance risks and side effects.

### 1.3.1 Osteoporosis and bone.

Osteoporosis can be literally translated as porous bones, leading to structural deterioration of the bone coupled with a reduction in bone density, increasing the risk of fracture [17]. With untreated osteoporosis, the quantity and quality of the

bone deteriorates and becomes more vulnerable to fracture at much lower forces than would normally be expected.

Primary osteoporosis is considered as a condition with non-modifiable risk factors, these conditions are predetermined, such as parental history of osteoporosis or hip fracture, age, gender, ethnicity, menopause prior to age 45 years and genetic susceptibility. Secondary osteoporosis is classified as osteoporosis caused by external factors, and therefore interventions can be used to alleviate risk. This includes lifestyle choices of excessive alcohol consumption, smoking, low body weight/BMI, inactivity and low bone mineral density, as well as other drugs and diseases known to affect bone metabolism.

Osteoporosis is the most likely cause of low trauma fractures in both men and women aged 80 years or older, and are classified as those fractures occurring as a result of a fall from standing height or less, of the femoral neck (hip), lumbar and thoracic vertebrae and distal forearm. In the age range of patients between 65 – 79 years, a femoral fracture at any site was an indicator of increased osteoporosis risk [18]. Previous fracture confers an increased risk of subsequent fracture, significantly increasing the risk of a hip fracture in both sexes, not allowing for independent risk factors such as lifestyle choices or medications [19]. A local fracture liaison service identifies these patients from imaging reports and invites those aged between 50 and 75 years to attend for DXA scanning, with a view to reducing subsequent fractures and allowing timely treatment of osteoporosis where found.

### 1.3.2 Osteoporosis treatments.

The use of bisphosphonate drugs to intervene in the process of bone loss through osteoclast suppression has been documented from the 1960's [20]. Such therapy also benefits conditions where bone turnover is imbalanced; hormone-induced bone loss – oestrogen and androgen deprivation [21, 22], glucocorticoid use [23], post transplant [24] and paralysis/spinal cord injury affecting weight bearing ability [25].

The World Health Organisation (WHO) define osteoporosis in men and postmenopausal women when the T score, acquired using DXA scanning of the femoral neck, is -2.5 standard deviations or more below the average measurement given for a young, healthy female [26]. It has been cited previously in a large scale meta analysis study [27] that there is over two times increased risk of hip and vertebral fracture for each decrease in standard deviation bone mineral density (BMD). Although these study cohorts were predominantly women, the authors felt the results translated equally well to the male population. These scan results are used as a guide to discussion and decision making in conjunction with the patient regarding treatment of osteoporosis, based on individual overall risk of fracture, as supported by the current NICE, SIGN and National Osteoporosis Guideline Group (NOGG) guidelines [28-30]. The guidelines do have slight variation in advice to UK healthcare professionals, with SIGN recommending the use of Q fracture to assess fracture risk, (NOGG) recommend the use of FRAX and assessment with either tool suggested by NICE. Recommended scan intervals for assessment of treatment are also dependent on the guideline utilised, with SIGN suggesting a three year scan interval for assessment of treatment[29], NOGG recommend treatment review at three years following the use of

intravenous Zoledronate and five years of oral bisphosphonate therapy [30], and NICE advocating reassessment of BMD following three to five years of bisphosphonate treatment [28]. These guidelines reflect the interpretations of the available evidence, and despite minor differences, the care and treatment of those with osteoporosis transcends specific guidelines, and is recognised as a world wide problem.

Anti-resorptive, or bisphosphonate drugs are used to treat low bone density and osteoporosis, and are the group of drugs most commonly used for the treatment of osteoporosis, taken over an extended period of time to aid the strengthening of the structure of bone tissue. Osteoporosis treatments are designed to strengthen the internal structure of the bone, inhibiting osteoclast function, which in turn inhibits bone resorption, leading to net gain in bone density.

Most commonly prescribed are nitrogen containing bisphosphonates: Alendronate, Risedronate, Zoledronate, Ibandronate and Pamidronate. Alendronate and Risedronate preparations are the most commonly prescribed osteoporosis drugs, designed to be consumed orally, and most commonly taken on a weekly basis to minimise inconvenience to patients.

Alendronate therapy is highlighted as the most commonly prescribed bisphosphonate, and therefore most likely to be associated with atypical femoral fracture [31-33]. It is approved for treatment of postmenopausal osteoporosis in women, glucocorticoid - induced osteoporosis and osteoporosis in men. Risedronate works on the same basis as Alendronate therapy, approved for treatment of osteoporosis in postmenopausal women to reduce the risk of hip and vertebral fracture, and in men. It is also indicated in the treatment of glucocorticoid - induced osteoporosis. Ibandronate is taken monthly as an oral preparation or a three monthly injection as a means to treat osteoporosis in

postmenopausal women with an increased fracture risk. With these therapies, a duration of five years is recommended, with continuation to ten years recommended in patients taking glucocorticoids ≥7.5mg per day, previous fracture history, or low trauma fracture whilst on treatment and age ≥75 years [34]. The drawbacks of bisphosphonate treatment can be related to poor compliance due to the nature of the prescription, intolerance due to short term and almost immediate reported side effects – stomach pain, oesophagitis and reflux, bone, joint and muscle pain, headache, uveitis and scleritis, bowel upset [35]. One study attributed 47.5% of non-persistence to adverse side effects, 40% to inadequate health literacy and just over 10% related to cost of prescription [36]. Zoledronate has a greater skeletal uptake, and a longer duration of action, but does have longer lasting flu-like side effects, potentially of several days when compared with bisphosphonate tablets, which are more likely to cause heartburn type symptoms which may last for several hours [37]. This may be more tolerable to patients as the Zoledronate infusion is annual and side effects ameliorated by the annual nature, and diminishing severity of potential side effects with each infusion given [38].

There is an increased risk of rebound vertebral fracture on discontinuing Denosumab, unless bisphosphonate therapy is initiated on cessation of therapy [39]. The risk increases at 3 months post cessation of therapy, with BMD at 12 months dropping to back to pre treatment baseline if no concomitant therapy is taken [40]. This is speculated to be as a result of BMD dropping by around 5% at both hips and lumbar spine, something which can be mitigated with the use of bisphosphonate medication. One study suggested that around 10% of patients studied suffered at least one fracture in the first year post Denosumab therapy, with all but one patient suffering from one or more vertebral fractures.

None of these patients were prescribed bisphosphonate therapy until after the fracture event [41]. Denosumab is known to have side effects related to hypocalcaemia, osteonecrosis of the jaw and skin/infection issues such as eczema and cellulitis.

Bisphosphonates work through the suppression of bone turnover by inhibiting the breakdown of hydroxyapatite, a mineral salt composed of phosphate and calcium, which is a key component of normal bone, providing rigidity and toughness to bones. Bisphosphonate drugs bind to hydroxyapatite crystals, as they have a high affinity to bone. Osteoclast apoptosis is encouraged by bisphosphonates, which in turn decreases bone resorption. This allows a relative increase in osteoblast activity, which gradually translates to increased bone mineral density. It is suggested that maximum suppression of bone resorption occurs at around three months following commencement of therapy [42], although a measurable change in BMD takes many more months [43]. Release of drugs from the bone is dependent on turnover rates and may remain in the bones for years following cessation of therapy. The renal system excretes any bisphosphonate released by the bone, but bisphosphonate is recycled within the bone [44]. Binding of bisphosphonates to the bone matrix occurs at different rates, Zoledronate is best, followed by Alendronate then Risedronate.

The action of Denosumab differs from bisphosphonate drugs, as it works by interfering with the receptor activator of nuclear factor kappa β ligand known as RANK-L system [45]. It does not attach to bone tissue, but rather binds to RANK-L in the circulation. Denosumab is a human monoclonal antibody, binding RANK L, preventing it from activating RANK, which is its receptor on the surface of the osteoclast. During this process, osteoclast activity is regulated by

RANK-L, produced by osteoblasts and osteocytes, which affects osteoclast survival rates, formation and function, as demonstrated in figure 1.5. As a consequence of this, resorption of bone slows and growth factors are released, which increases osteoblast numbers and activity. Osteoclasts also directly regulate osteoblasts via cell to cell contact and secreting additional factors [45].

Figure 1.5. The action of Denosumab within bone. Figure removed by author of this thesis for copyright reasons

Denosumab has a rapid onset and offset of action, having a half-life of anywhere from 25-32 days [46], and has been shown to increase cortical bone mass at a greater rate than Alendronate, with no plateau in BMD gains after an extended treatment duration as seen with Zoledronate [47, 48].

## 1.4 Hip fractures

Hip fractures typically occur as a consequence of falls in the older individual, affecting around 65,000 people in the United Kingdom (UK), at a cost of approximately one billion pounds per year, expected to rise to £1.5 billion by 2025 [49, 50]. The mean age of patients suffering typical hip fracture has been quoted as 76.5 years in some research [51, 52], although another study found the average age to be significantly higher at 82 years [53], and the National Institute for Health and Care Excellence (NICE) state the average age of to be 77 years [54]. Patients typically present with the affected leg externally rotated, with apparent discrepancy in the length of the leg [55].

The treatment options for hip fracture are dependent on the fracture location, as identified by the NICE hip fracture quality standards [49, 54] and Scottish Intercollegiate Guidelines Network (SIGN) guidelines [56]. Displaced fractures located within the capsule of the hip (intracapsular fractures) are treated with cemented hemiarthroplasty, with the option to have a full hip replacement if clinically justified. Fractures at or above the level of the lesser trochanter should be treated by hip screw or other external bone fixator, in preference to intramedullary nailing.

### 1.4.1 Morbidity and mortality of hip fracture.

According to the works of Schnell [57], patients who suffer a hip fracture are 75% more likely to be female, with a mean age of just under 85 years. The relative risk of mortality and ageing associated with hip fracture increases by around 4% per year, with around half of patients requiring greater levels of care, whether that is with assisted living or requiring admission to a care facility.

Long term limitations in mobility, self care and activities of daily living following hip fracture, along with quality of life are suggested as main reasons for requiring assistance [53]. The risk of mortality is below two percent in patients under the age of 70, but is over 25% in patients over 90 [57]. The cost of all UK hip fractures was estimated at around £1 billion in 2011, covering medical care only with around 30% of all hip fracture patients dying within the first 12 months post fracture [49]. A caveat is mentioned within the same document however, that many of the patients not surviving one year post hip fracture died of associated health conditions, not primarily as a consequence of fracture. All guidelines advocate fracture assessment of affected patients, with those under 75 years generally referred for DXA scanning and those over 75 years to be discharged with bone strengthening medication [28, 29].

### 1.4.2 Population demographics.

It is estimated that by 2043, the population of Scotland aged 65 years will increase by over 23%, exceeding 633,000, with all age groups over 65 years identified as broadly increasing in numbers over the same timescale, as demonstrated in figure 1.6 [58, 59]. The life expectancy of average male is given as 80.6 years and female 83.8 years [60]. The United Kingdom (UK) national prediction for the growth in the population of over 65's by 2069 is around 8.2 million, with populations in each area of the UK increasing steadily due to extended life expectancy. With an ageing population comes an increased risk of fracture, this is the focus of osteoporosis therapy; to reduce fracture risks. One in two women and one in five men will suffer from a fragility fracture in their lifetime (National Osteoporosis Society 2015). The costs of hip fracture care in hospital alone amounts to over £14,000 per patient in the first

year post fracture [61]. Following this, 9.4% of patients will die within the first 30 days, 31.2% will not survive the first year, almost 20% of patients will be admitted to a care facility, and for patients who suffer a second hip fracture this figure rises to 40% by one year post fracture [61].

Figure 1.6 Population prediction pyramid of Scotland 1981 – 2043, demonstrating an increase in the over 65 population. Fiogure removed by author of this thesis for copyright reasons.

A forecasted 29% increase in hip fractures within the same age group [59] suggests the incidence and therefore the cost of osteoporosis and hip fractures to the National Health Service (NHS) is likely to increase significantly. Hip fractures are debilitating, and impact hugely on the quality of life in the long term for the patient – women are three times more likely to fracture a hip than men, with mortality rates at one year post hip fracture between 22% and 29% [62]. Around 20% of hip fracture patients will require admission to long term care [63].

Almost 50% of total fracture cost to the NHS in the UK can be attributed to hip fracture, at over £2000 million [64]. Men are more likely to fracture at a younger age than women, 79 years compared to 82.7 years, and are more likely to die within a year [62]. These statistics are broadly comparable across the western world and therefore transferrable to healthcare services in these areas.

## 1.5 Osteoporosis risk factors.

### 1.5.1 Diabetes Mellitus.

Association between diabetes mellitus (DM) and fractures, including AFF, appear to be linked to microvascular bone damage [65]. There is agreement across research that there is a significant increase in fracture risk in patients diagnosed with diabetes mellitus (type 1 and 2) [65, 66]. Diabetes mellitus, both type 1 (T1DM) and type 2 (T2DM) have implications for BMD and fracture risk, specifically linked to subtrochanteric and diaphyseal fractures, with Caucasian women found to be at three times higher risk of these fractures if diabetic [67]. No data was collected on the diabetic status of the patient group scanned, but around 7% of the population of the UK are thought to suffer from diabetes [68].

In one study, observers found it difficult to separate T1DM and T2DM, as insulin dependence factored in both groups [69]. It was observed that one in 15 T1DM patients would be likely to suffer a hip fracture by the age of 65 years [69], and to be on average five years younger than T2DM hip fracture sufferers [70]. Measurement of BMD at lumbar spine in T1DM is likely to be lower than age-matched contemporaries [65, 71], while in T2DM patients BMD is likely to be higher than age matched controls, but with increased fracture risk [65, 72]. This is posited to be as a consequence of microvascular bone damage [66], perhaps

linked to peripheral neuropathy [66, 70], although this suggestion was refuted in another study [71]. An artificially elevated BMD, thought to explained by micro architectural abnormalities, appears to underestimate the fracture risk in T2DM patients [65], while there also appears to be a link between low Vitamin D status and T2DM [65, 66]. Assertions are also made that thiazolidinedione medications used to manage T2DM can increase risk, where metformin and sulfonylates reduce fracture rate and maintain or improve bone mineral density [66].

No indication was found to suggest any issues with healing or non union of surgically repaired hip fractures, but T2DM patients required on average four days longer inpatient hospital care [70]. It has been suggested that diabetes is a strong risk factor for AFF by several authors [51, 73-77] and further research is indicated to understand the specific reasons behind this.

### 1.5.2 Thyroid.

There is a general acceptance in the literature that undiagnosed/untreated hyperthyroid leads to two fold acceleration on bone loss, increasing fracture risk [78, 79]. It is speculated this is as a result of calcium malabsorption, eventually leading to an increase in bone resorption [80]. A history of hyperthyroidism has been indicated as an independent risk factor for both hip and vertebral fracture [79], and even with treatment, BMD and fracture risk may never return to a normal range [78]. The findings of one study suggest that those with hypothyroid may also be at increased risk of fracture, hypothesising that there is an increased risk of osteoporosis and related fractures, especially in the 60-79 years age group [81]. Thyroid hormone requirement decreases with age, therefore poorly monitored and balanced thyroxine prescription potentially leads

to increased risk of thyroxine induced hyperthyroidism [81]. This is in contradiction to another study, which found no evidence of detriment to BMD at any site with thyroxine therapy, however this information was gathered over a one year period of treatment [82]. A possibility was mooted of reduced BMD at the wrist in premenopausal women, with no suggestion of an associated additional fracture risk [82]. The use of hypothyroid medication has been linked in association with AFF [31, 74, 78], which is attributable to 18.8% of the patient population scanned. No mechanism for increased fracture risk has been specifically identified, with the exception for oversupply of thyroxine in patients who have not had levels checked regularly [81].

It is speculated that accelerated bone turnover is a consequence of untreated hyperthyroidism, with a figure of 10-20% loss in bone mineral density, mainly from cortical bone [78]. There appears to be residual risk of BMD not returning to expected normal with treatment, in a small number of patients [78]. There is little evidence to support thyroxine having an adverse effect on BMD where replacement therapy is tested and kept to minimum levels, but increased risk where thyroxine is over supplied through poor monitoring [78, 83].

### 1.5.3 Anti-oestrogen therapy.

Aromatase Inhibitors (AI) such as Letrozole, Exemestane and Anastrozole are commonly prescribed as a treatment for breast cancer, with the intention of reducing oestrogen levels by around 90% [84]. Medication is usually prescribed for a duration of five years, with many now extending to ten years of therapy to reduce the risk of breast cancer recurrence. Such extended oestrogen-blocking treatment also potentially has a detrimental effect on bone mineral density, as bone is oestrogen dependent. This oestrogen deficiency is responsible for

increased osteoclast activity and bone remodelling, in a state of higher bone turnover and accelerated bone loss, the rate of bone loss is approximately doubled in post menopausal women by the use of these drugs [85]. Evidence suggests that patients with a normal BMD at commencement of treatment with AI will subsequently have a normal bone mineral density at five years of therapy [86]. However, if the BMD is reduced at commencement of therapy, there is an increased risk of osteoporotic fracture after three to five years of treatment [86].

### 1.5.4 Androgen deprivation therapy.

Androgen deprivation therapy (ADT) is used to reduce the circulating levels of testosterone, leading to bone loss and increased risk of fracture, especially hip and vertebral [22, 84, 86, 87]. These drugs are a recognised treatment for prostate cancer, and known to cause almost immediate hypogonadism, leading to rapid bone loss in the first 12 months of therapy [22]. It is suggested that around 20% of patients using this therapy will sustain a fracture within 5 years [87]. The same author suggests treatment thresholds be lowered for such patients, based on this increased risk. There appears to be agreement that current evidence does not indicate additional risk of AFF in conjunction with ADT, but acceptance that there is no evidence on background incidence of AFF [87].

### 1.5.5 Proton Pump Inhibitors.

Proton Pump inhibitors (PPI) are used to reduce the secretions of acid within the stomach in order to reduce symptoms gastric ulcers and gastro-oesophageal reflux. It can also be utilised to give protection to the stomach whilst taking non steroidal anti inflammatory drugs (NSAID), glucocorticoids,

bisphosphonates and other medications which may cause stomach problems, making it complex to separate any detriment to bone specifically linked to PPIs [88-91]. PPIs suppress the production of gastric acid, which causes interference with the absorption of calcium, as lower levels of gastric acid reduce the amount of calcium which is dissolved and ionised within the stomach. An increased pH within the stomach reduces the amount of calcium which is dissolved and rate of absorption is slowed, by as much as 65% [92, 93]. This is postulated to result in calcium malabsorption, and therefore potentially resulting in a net reduction in bone mineral density [89]. The body's ability to absorb calcium also decreases naturally with age, and the response to this is to increase the production of parathyroid hormone, giving rise to secondary hyperparathyroidism. This increases osteoclastic bone resorption which diminishes and undermines the internal bone structure, increasing the potential for fracture [93].

There is a suggestion that decreased calcium absorption coupled with stomach acid pH increase associated with PPI use could be responsible for a form of malnourishment [92]. The same study indicated an increased risk of any fracture in the first year of use, and increased hip fracture risk in subsequent years with prolonged PPI exposure [92]. In support of this assertion, others have cited increased risk of hip fracture in those taking regular PPIs, however they suggest this is owing to confounding factors unrelated to osteoporosis [89, 90]. In contrast to these findings, other studies suggest that PPI has little or no association with BMD at either hip or spine [88, 94]. Statistics suggest that PPIs are in the top 5 most prescribed drugs in the western world [89], and are most likely to be prescribed in areas known to have poor social and socio-economic status [90].

There is evidence within the literature which appears to identify an increased risk of hip fracture with PPI use [88, 90, 91, 93-95], and some studies identified a link between PPI and subtrochanteric and femoral shaft fractures [67, 96]. However, with further detailed analysis of the figures, all agree that the association of hip fracture risk and PPI are due to unmeasured confounding factors. Further to this, there appears to be no detrimental effect on DXA-measured bone mineral density with the use of PPI, even if the use is prolonged [88, 91]. With no causal links between PPI and reduced BMD identified it can be assumed that, until further evidence is produced, PPIs do not have a detrimental effect on bone health and are not linked directly with increased risk of fracture [91, 93, 94].

### 1.5.6 Glucocorticoids.

It has been widely identified in literature that glucocorticoid use increases the risk of fracture, including risk of AFF [16, 31, 97, 98]. Glucocorticoid medication is prescribed for a wide range of inflammatory conditions, and the effect on the gastrointestinal system and on bone turnover means bisphosphonate drugs and PPI are often prescribed in conjunction, making it more difficult to separate individual causes of AFF [51, 99]. Glucocorticoids influence bone density in several ways; by inhibiting formation of new bone, stimulating osteocyte and osteoblast apoptosis, reducing growth factors which stimulate osteoblasts leading to net bone loss. This is especially in the early stages of treatment when doses are higher and disease processes more active [100]. This is compounded by the reduction in calcium absorption coupled with the raised excretion levels of calcium in the urine [101, 102]. Vertebral fractures are more common than hip fractures in patients prescribed with long term glucocorticoids

[102], but there is increased fracture risk at all sites [100]. Several studies have reported higher risk of atypical femoral fracture with long term glucocorticoid use, but accept that most of the patients concerned were also having concomitant anti-resorptive bone therapy [31, 99, 100, 103]. In one study, six iAFFs were identified in patients with autoimmune disease, bisphosphonate use and glucocorticoids, using x-ray over a period of two years, similar to the data collected within this department [99]. The same authors also found 15 incidences of beaking at the inception of the study, affecting 8% of the study population. This presents a difficulty in defining whether bone strengthening treatment or glucocorticoids are the specific cause of AFF, and empirical therapy as recommended by both NICE and SIGN may compound this problem [28, 29].

### 1.5.7 Selective Serotonin Reuptake Inhibitors.

It is generally accepted that Selective Serotonin Reuptake Inhibitors (SSRIs) have a negative impact on bone mass, and although the pathophysiology of this is not fully known, there is a known association between depression, fractures and falls risk [104-106]. The risk appears to increase over time, and with the severity of the depression. Serotonin blocking has the effect of lowering bone mass, therefore SSRIs should lead to increased bone mass, but the available evidence contradicts this hypothesis [104]. Depression and osteoporosis share many risk factors; smoking, alcohol consumption, poor nutrition leading to weight loss and lower BMI, reduced physical activity leading to sarcopenia, increasing falls risk and lack of exposure to sunlight leading to lowered levels of Vitamin D [107]. It is widely accepted in the literature that depression and SSRIs have a negative association on BMD and falls risk [105, 106, 108], with

increased risk of both hip [109, 110] and vertebral fracture [111], especially in conjunction with other chronic illnesses, which may induce falls [112].

Some studies failed to identify BMD levels in the osteoporotic range, suggesting other factors may be at least partly responsible for fractures in patients taking long term SSRIs [113, 114], however this is not consistent with other findings, which found association between SSRIs, low BMD and increased fracture risk [115, 116]. There is consensus in the literature that further in-depth research is required in order to identify drug interactions, medical conditions, risk factors and effective osteoporosis therapies should they be required.

### 1.5.8 Anticonvulsants and osteoporosis.

Epilepsy affects around 1 in every 100 people in the developed world [117]. The evidence suggests that patients with epilepsy are at increased risk of fractures and osteoporosis. The use of anticonvulsants in the treatment of epilepsy has been demonstrated to affect the absorption of both calcium and Vitamin D [118]. Low levels of serum 25(OH)DV has been associated with increased risk of hip fracture, in patients with and without epilepsy [119]. The findings of one study indicated fracture risk in epilepsy is independent of BMD [120], and commonly patients will suffer vertebral fractures as a consequence of seizure activity [121].

Co-morbidities in epilepsy are high, such as cerebral palsy, post brain surgery or injury, post stroke and physical disability causing balance issues, muscle weakness and falls, all contributing to increased fracture risk [118, 122]. The type and duration of epilepsy also influences BMD [122]. It has been identified

that BMD loss in men taking anticonvulsants can be ameliorated with the combination of Risedronate and Calcium/Vitamin D supplementation taken over a period of two years [123].

### 1.5.9 Family history of osteoporosis and genetic links.

There is increased personal risk of osteoporosis if a familial element has been identified. This can lead to a two fold increase in risk of fracture in comparison with someone with no family history of osteoporosis [124]. This may be as a consequence of environmental similarities, or genetics, or a combination of these. There is evidence that proximal hip BMD is greatly influenced by genetic factors [125]. A history of low BMD measurement in a sibling places any individual at around six times greater risk of low BMD themselves [126]. Genetics and BMD is a very complex area, which is currently an area of interest with regard to both osteoporosis and also AFF. There are around 60 genes with known association to BMD, with the most studied being the Vitamin D receptor (VDR) gene [126]. Work by a team in the Middle East has indicated a link between osteoporosis and the VDR gene [127]. The same research also identifies a need for more focused in-depth analysis of identifying genetic markers of osteoporosis, as no definitive association between VDR and fracture or indeed BMD has been proven [127, 128]. A meta-analysis of genetic susceptibility of fracture risk and BMD found 15 distinct genetic links to both fracture and BMD, but not to low Vitamin D levels [129]. It is speculated that genetics influence as much as 90% of inherited BMD, including 39 % increased risk of low BMD at femoral neck in affected siblings [130].

As AFF appears to be heavily associated, though not exclusively, with the use of bisphosphonate drugs, it would be assumed that all consumers be at similar

risk of developing a fracture related to the drug. This is clearly not the case as AFF is a rare, but significant, event and as such this suggests there are other confounding factors which increase the risk, one of those being a genetic susceptibility [103]. Several studies were identified which attempted to identify genetic links to AFF, a highly complex field. A study of three sisters found some gene mutations in common with AFF (GGPS1 and CYP1A1), although the same mutation was found in an unrelated person with AFF [131]. The authors speculate that an accumulation of several genetic variants/mutations may lead to susceptibility to AFF, given its rare presentation. A further familial study failed to find a specific genetic mutation which could be responsible for AFF, suggesting a combination of factors, including genetics and environment, be responsible [132]. A further genetic study found a link between COL1A2 and AFF [133], however the significance of this finding was unclear. Recent works on genome-wide association studies (GWAS) have identified 30 potential causal genes which have been demonstrated to influence BMD [134, 135]. As such, difficulties exist in provision of a comprehensive genetic screening programme which would better predict patients at risk of AFF linked to bisphosphonate exposure, but ongoing research has the potential to enable targeted testing to minimise risks of AFF from bisphosphonate exposure [134, 136]. Also more commonly linked to these genetic profiles are Osteogenesis Imperfecta [137], hypophosphatasia [138] and osteopetrosis [139], complicating identification of bisphosphonate as the sole mechanism of damage to the femoral cortex. There is acceptance across the literature available that further case-control research is required on an international scale to identify variants, both common and rare, which may be associated with osteoporosis and AFF [126, 127].

### 1.5.10 Conditions known to influence bone density.

#### 1.5.10.1 Smoking

Lifestyle choices of smoking and alcohol intake influence BMD, smokers have an increased risk of fracture, which diminishes on stopping, but not to non-smoking levels. The inhalation of toxic chemicals causes an imbalance in bone turnover, leading to net bone loss, and also having an indirect influence on BMD through BMI, parathyroid and sex hormones and oxidative stresses [140]. Smoking has the potential to decrease the hormone levels of both sexes, especially oestrogen levels of women, giving a tendency toward reaching menopause up to two years earlier than non smokers [141], negatively impacting on bone mass, with evidence indicating the toxins released by smoking tobacco increases the production of oestrogen destroying enzymes, which has a direct impact on bone density [142]. This is especially true at the hip area, with one study quoting a 40% increased risk to male smokers of hip fracture, and 31% for female smokers [143]. The cessation of smoking has demonstrated improvement in BMD and a reduction in fracture risk [144], however as the effects of smoking are cumulative, fracture risk reduction does not happen immediately. The commencement of tobacco smoking in adolescence has been shown in one study to reduce peak bone mass accrual, leading to lower BMD levels in later life [145], this claim was refuted by another [141], who suggested that no significant impact was found on bone health in smokers under the age of 40.

#### 1.5.10.2 Alcohol

Alcohol intake greater than the UK Government recommended levels of 14 units per week can also impact BMD. A study has shown that alcohol intake women

aged over 67 years detrimentally impacts on bone health, having a negative impact on bone formation rates. Alcoholism is known as a major cause of secondary osteoporosis [146] and hypogonadism in men [147], and increased risk of falling [148]. In contrast, a small amount of alcohol is considered to have a neutral or even beneficial effect on BMD, depending on the type of alcoholic drink chosen, especially in post-menopausal women [148]. Of concern is the impact of binge drinking (6 or more units per day) on the BMD of younger people, where alcohol intake will potentially have a greater impact on hormone levels and consequently on BMD in the longer term [142, 146, 148].

Alcohol excess can affect liver function, which in turn can affect the metabolism of Vitamin D from the diet. Cirrhosis of the liver is a risk factor for osteoporosis, with one study suggesting that 90% of patients with alcohol-related cirrhosis are Vitamin D deficient [149].

#### 1.5.10.3 Vitamin D

Adequate Vitamin D is required to aid the absorption of calcium, required for bone heath. Vitamin D has also been identified as playing a critical role in the maintenance of muscle health, which in turn has an impact on falls risk [142].

One study found that almost 75% of patients presenting with hip fracture were Vitamin D deficient, and over 80% were osteoporotic or severely osteoporotic [150]. Persistent Vitamin D deficiency is also linked to osteomalacia, a sub-clinical lower bone mineral content, which can also lead to increased risk of fracture. Around a third of the UK population aged between 19-64 years are considered to be Vitamin D deficient during the winter months, and supplementation of 10µg of Vitamin D should be considered by everyone aged

four years and over [151]. Vitamin D deficiency was identified within several studies as a finding of those with AFF [152-154].

#### 1.5.10.4 Calcium

Calcium supplementation has traditionally been prescribed in tandem with bisphosphonate medications, in a bid to reduce the risks of hypocalcaemia and allow the efficient mineralisation of new bone formed [155]. The intake of dietary calcium or supplementation of calcium leads to a directly proportionate fall in circulating parathyroid hormone, which has a short term impact on BMD [155]. At the formative stages of peak bone mass, links have been made between calcium intake at adolescence and adult BMD [156]. The evidence to support dietary supplementation is contradictory, where the benefits of calcium supplements appear to be greatest in the elderly who are at increased risk of hip fracture, and those who are institutionalised [156], however this group is also more likely to be deficient in Vitamin D and have a low dietary calcium intake [142, 157]. There are drawbacks to calcium supplementation, with gastrointestinal upset being commonly reported, along with an increased risk of renal calculi [158]. Anecdotal evidence gathered from clinical practice suggests patients do not adhere to the calcium and Vitamin D treatment regime prescribed, for some the tablets taste bad, leave a chalky residue in the mouth or cause digestive upsets and excessive flatulence, findings also supported in a previous study [159]. Others report that the “swallow whole” calcium and Vitamin D preparations are too bulky to swallow, leading to choking, and if broken in half are prone to sticking in the throat, similar findings were reported in a USA study of dietary supplementation, leading to guidelines on capsule size [160].

#### 1.5.10.5 Malabsorption of nutrients

Malabsorption of nutrients – specifically calcium and Vitamin D can also lead to primary hyperparathyroidism, a condition causing continuous excessive secretion of parathyroid hormone, predominantly affecting cortical bone [161]. Untreated, this has the potential to reduce bone mass and increase fracture risk [162]. A study comparing BMD measurement with trabecular bone score (TBS) identified a degraded bone structure in over 50% of patients with hyperparathyroidism, yet only 37.5% of which were diagnosed with osteoporosis, identifying a discrepancy between measuring bone quality and quantity [163].

Coeliac disease (CD) is triggered by an immune response to gluten in the diet, thought to affect 0.5-1% of the world population [164], caused by gluten intolerance, and can contribute to osteopenia and osteoporosis. In around 70% of cases BMD will be adversely affected in patients at time of CD diagnosis [165], as a consequence of malabsorption of nutrients caused by villous atrophy in the small intestine [166]. This leads to lower absorption rates of dietary calcium, however these effects are potentially reversed when a gluten-free diet is strictly followed. Fracture risk associated with CD appears to be minimally increased, and BMD appears to improve after one year of a strict gluten-free diet with no additional supplementation [167], however a minority will not achieve normalisation of BMD [168].

#### 1.5.10.6 Body Mass Index (BMI).

There is a general consensus within the literature that low body weight and malnutrition adds to risk of osteoporosis. These known risk factors for

osteoporosis can present as consequences of an eating disorder such as Anorexia Nervosa (AN), and have the potential to impact negatively on BMD, and increased fracture risk, especially at the hip [169-172]. One study indicates that over 90% of AN patients studied had significant bone loss in at least one skeletal site, and less that 15% of patients had a BMD in the normal range at all sites [173]. Risk of fracture increases and remains increased for many years post diagnosis of AN [169]. Oestrogen replacement therapy at higher levels similar to HRT has been indicated as being beneficial to BMD [170], and while most studies support the assertion that oestrogen deficiency related to AN may lead to bone loss, there have been studies which suggest oestrogen replacement through oral contraceptives does not appear to markedly improve BMD [171-173]. This may be as a consequence of the uncoupling of bone formation and absorption, caused in part by malnourishment [174]. Lower BMI and BMD than age matched contemporaries puts AN sufferers at increased risk of hip fracture and greater risk of osteoporosis [174], a BMI below 20kg/m² is associated with increased fracture risk [175].

A BMI measurement of over 40kg/m² is considered as morbidly obese and adds a considerable heath burden to the cardiovascular system, increasing the risks of Type 2 diabetes mellitus, heart disease and stroke, and reduced life expectancy [176]. Elevated BMI has also been identified as a risk factor for AFF, however this is complicated by concomitant glucocorticoid use [73]. The increased BMI measured in some patients can provide challenges in undertaking a BMD examination, affecting the reproducibility of the measurements, providing the patient weighs less than the weight restriction of the scanner.

### 1.5.11 Rheumatoid Arthritis.

Rheumatoid arthritis (RA) is an auto-immune disease inducing an inflammatory process of the synovium causing joint destruction, accompanied by swelling, stiffness and pain which may severely limit patient mobility and activities of daily living [177], known to affect around 1% of the population and predominantly diagnosed in women [178]. Patient immobility as a consequence of the disease process and treatment with glucocorticoid drugs to reduce inflammation is known to cause osteoporosis in those diagnosed with RA, which in turn increases fracture risk [179]. However, it has been identified that RA increases fracture risk independently of glucocorticoid use or BMD [30]. While glucocorticoids may have implications in reducing BMD they can improve joint pain and inflammation, enabling a greater level of physical activity which in turn has a positive impact on BMD. One study identified almost 80% of RA patients as reliant on low-dose glucocorticoids to remain mobile and active, and femoral neck BMD was not adversely affected by glucocorticoid use in the early stages of disease, however by 10 years post diagnosis the BMD at femoral neck had fallen below that of the control group [180].

### 1.5.12 Hormones and hormone replacement therapy.

Oestrogen is widely recognised as a protector of BMD and as such there is an anticipated drop in BMD at menopause, with the greatest effect on BMD being recorded in the first decade post menopause. The lack of oestrogen if menopause is reached before the age of 47 years has been demonstrated to increase risk of osteoporosis, fragility fracture and mortality [181]. The significance of oestrogen begins at menarche, with earlier age of menarche resulting in generally higher oestrogen levels, reduced fracture risk and

increased BMD. Fewer years of menstruation and osteoporosis are directly linked [182]. This also affects patients with severe eating disorders where sex hormones are suppressed [183], and low BMI, which is also considered a risk factor for hip fracture [30]. [184]. It may be useful to offer HRT as bone support in women with premature ovarian insufficiency and premature menopause, although all benefits are controlled by dose and duration of therapy. One recommendation suggests it should be used where tolerated to at least age 51, but with no arbitrary limit set on upper age of use [184]. The use of HRT may provide an early treatment solution for bone loss, sparing bisphosphonate therapy for later years [185].

Hypogonadism in men can be treated with testosterone hormone replacement therapy to supplement the low level of circulating testosterone in the body, which can alleviate symptoms while also improving BMD [186, 187]. Low testosterone levels have been linked with alcohol excess, chronic infection such as HIV, steroid treatment, and chronic liver disease; as many as 50% of diabetic men may suffer from hypogonadism [187], and are more likely to be obese [188, 189]. The increased risk of osteoporosis in untreated hypogonadism is overcome with testosterone replacement therapy along side bisphosphonate drugs where necessary. The links between hypogonadism and osteoporosis are by association, not causation, owing to a paucity of studies of testosterone therapy in men with proven osteoporosis [187].

Characteristically osteoporosis-related fragility fractures occur at the wrist, hip, humerus, pelvis and spine. Sustaining a fragility fracture almost doubles the risk of sustaining a further fracture, and this risk is doubled again if the fracture is vertebral - independent of BMD measurement. Almost half of all subsequent

fractures will occur within five years of the incipient fracture [161], indicating a window of opportunity for treatment to reduce fracture risk. Around half of all hip fractures occur in patients who have already suffered a fragility fracture [190], and family history of hip fracture is known to confer additional fracture risk, again independent of BMD [30]. When patients are imaged in Accident and Emergency following fracture, osteopenia is rarely mentioned in the subsequent imaging report, and less than 20% of patients are given information regarding bone health, either with information regarding diet and lifestyle or with referral for DXA scanning [161]. One study indicated around 50% of patients scanned using DXA fell in the osteopenic category [191].

### 1.5.13 Transplantation.

Transplantation of donor organs generally induces a drop in BMD, especially in the first year post transplant, possibly as a consequence of immunosuppressant therapy, lack of mobility, treatment effects of chronic disease and end stage organ failure, which may predate the transplant. Increased fracture risk continues for 10 years post solid organ transplant, with the exception of bone marrow recipients who have a reduced fracture risk after 5 years [192]. The exact mechanism for this is unknown, but may be as a result of anti-rejection medications, a consequence of poor mobility in end stage organ failure pre transplant or as a combination of several factors.

### 1.5.14 Anti-retroviral therapy.

Anti-retroviral therapy used in the treatment of HIV and AIDS has been demonstrated to reduce bone mass in long term therapy, with BMD being adversely impacted for up to two years post commencement of anti-retrovirals

[193]. This is pronounced in the use of Tenofovir, which is also used in the treatment of Hepatitis B [194]. The mechanism of bone loss has not been established definitively, although it appears women are more severely affected by the interactions of anti-retrovirals, hormones, BMD and the disease process of HIV [195]. There have also been indications that different combinations of medicines can lessen the impact on bone loss, with benefits seen in osteoporosis and also in renal function [196, 197]. Additional fracture risk has also been identified, primarily at the wrist and spine of both sexes and at the hip in men, and increasing with age [174].

## 1.6 Summary

This section has sought to provide a background to bone biology, osteoporosis, treatments and associated risk factors. The following section provides an overview of atypical femoral fractures and contributing factors as supported by the current literature, and the use of DXA in the diagnosis and monitoring of iAFF.

# 2 Atypical femoral fracture - literature review.

This chapter sets out the current knowledge of atypical femoral fractures presented in published literature, their aetiology and currently speculated risk factors.

## 2.1 Search strategy.

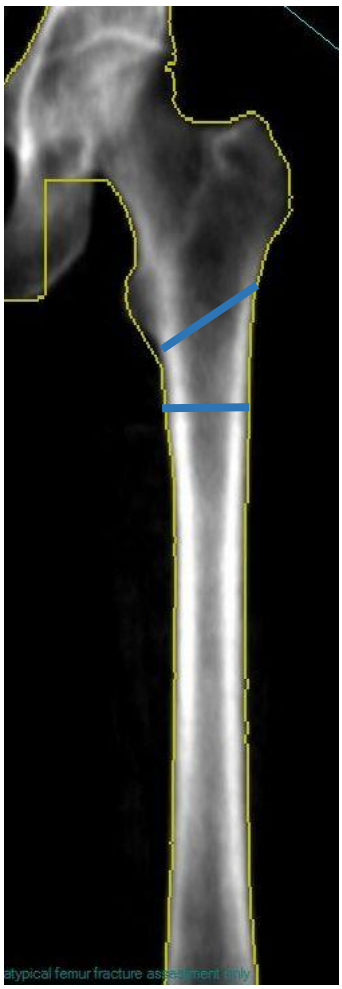
A literature search was conducted using Science Direct, PubMed, EBSCO, and Open Athens, using the NHS Knowledge network login. Search terms are listed in table 2.1.

Table 2.1 Search inclusion and exclusion criteria.

| Inclusion criteria | Exclusion criteria |
|---|---|
| DXA | Dysplasia |
| Atypical femoral fracture | Osteonecrosis |
| Latent beaking | Paget's disease |
| Thyroid | Malignancy |
| Glucocorticoids | |
| SSRI | |
| PPI | |
| Anticonvulsant | |
| Lifestyle choices | |
| Rheumatoid arthritis | |
| HIV and AIDS | |

## 2.2 Atypical femoral fracture.

Atypical femoral fractures are differentiated from these standard fractures by the presence of fracture in the absence of trauma, increased cortical thickness in many cases, and originate in the lateral cortex of the femur. Atypical femoral fracture, is classified in figure 2.1 as being extracapsular, not affecting the hip joint, and at the level the subtrochanteric area or below.



Subtrochanteric fracture site, below both lesser and greater trochanter.

Femoral shaft fracture site, considered to be anywhere from 5mm distal to the lesser trochanter to just proximal to metaphyseal flare (not to scale).

Figure 2.1 Atypical femoral fracture classification based on location.

First case reports prepared in 2005 suggested an association with these subtrochanteric low impact fractures with antiresorptive therapies, in particular bisphosphonate therapy [1]. In 2010 the American Society for Bone and Mineral Research (ASBMR) produced a consensus statement [198] on what constituted an atypical femoral fracture, later revised in 2014 [199].

Classification of atypical femoral fracture currently requires four of five of the following major criteria to be met [199]:

1. Fracture occurs with minimal or no trauma
2. Predominantly transverse fracture line, originating from the lateral cortex, may become oblique as the fracture progresses across femur medially.
3. Extends through both cortices and may be associated with medial spike as a complete fracture, or involving only the lateral cortex as an incomplete fracture.
4. Non-comminuted or minimally comminuted fracture.
5. Displays localised periosteal or endosteal thickening, known as beaking, of the lateral cortex at the fracture site.

Minor criteria which may be present but not essential for classification of atypical femoral fracture:

1. Cortical thickening of the femoral shaft.
2. Prodromal pain preceding fracture – unilateral or bilateral.
3. Bilateral incomplete or complete diaphyseal femoral fractures.
4. Delayed fracture healing.

There appear to be limited data published on the relationship between men and atypical femoral fracture, as the majority have focused on female patients [75, 98, 200, 201], supporting findings that women were 75% more likely to suffer from AFF than men [33]. However in most studies which have documented male inclusion, the rates of male involvement are small at 5% [52], 4% [202] and 12% [1]. A study conducted by Schilcher, published in 2015 found that around 5% of women and 1% of men taking bisphosphonates would suffer atypical femoral fracture [33]. Incidentally, the study reporting the highest level

of male involvement of atypical fracture was a seminal work in the field [1], which should have encouraged others to consider it a condition affecting both sexes.

This has prompted further research to determine incidence and potential underlying causes of atypical femoral fracture. While this is not fully established, recent research indicates the importance of length of bisphosphonate exposure [31, 75, 76, 200], concomitant glucocorticoid therapy [31, 97], Asian ethnicity [32, 97] and hip geometry/bowing deformity [76, 201, 203] are all relevant risk factors.

Atypical femoral fractures are typically transverse in nature, frequently with medial spike, and are sub trochanteric or diaphyseal in location. There is also a much higher possibility of fracture being bilateral than in typical fractures, with a reported increased risk of between 25% to 50% [2, 203] of contralateral fracture, especially when additional pressure is applied due to reduced weight bearing in the fractured limb [204].

Evidence exists of contralateral fractures being identified after intramedullary nailing of an atypical femoral fracture. It is speculated that this occurs as a consequence of additional stress from increased weight bearing placed on the non-fixed femur. This may go some way to explaining the bilateral nature of atypical fractures in up to 50% of sufferers, as additional weight bearing is expected of the non-painful limb [32, 204]. It is also suggested that higher activity levels in younger patients places the femoral shaft under greater cumulative stress, offering a partial explanation for the increased likelihood of AFF in patients aged 40-60 years, and the regularly observed bilateral nature of said fractures [99].

In contrast to typical fractures, atypical femoral fractures occur below the level of the subtrochanteric area, affecting the diaphysis of the femur. These have been recorded as occurring in a slightly younger age group of patient – mean age reported as 73 years [52], 75 years [51], and around 10 years younger than those with typical fractures [202]. This type of fracture tends to atraumatic, indeed, it has been reported that patients feel the fracture occurs and causes a fall, rather than the fall instigating the fracture as is reported in typical fractures. Atypical femoral fractures may also be preceded by prodromal pain in the groin or upper thigh, reported by patients as occurring from one week to two years preceding fracture [31, 97]. This has been reported as occurring in anything from 30% to 90% of patients with atypical femoral fracture [31, 75, 76, 98]. In contrast however, some studies report few participants reporting prodromal pain prior to fracture, and having similar figures of pain reported in fracture and non-fracture groups [76, 99, 205].

Links have been identified with area of maximal tensile loading and atypical femoral fractures, identifying hip and femur geometry as contributing to fracture risk. It is speculated that bowing deformities are more commonly found in Asian women [32, 75, 203] with concurrence that femur geometry is a confounding factor in atypical femoral fractures. Reasons for this include smaller bone size, shorter hip axis length and a larger varus angle of the femur [203]. There is a suggestion that there is an 8:1 increased risk of fracture in Asian women compared with Caucasian women [203]. As previously identified, there is a paucity of study data which include males as subjects, with many investigating atypical femoral fractures retrospectively. Currently there have been no links

made that indicate causation of atypical femoral fracture with the use of osteoporosis therapy [32, 203, 206].

## 2.3 Atypical femoral fractures and osteoporosis treatments.

A positive association has been identified between treatment adherence and risk of AFF [200]. This study indicated findings of reduced risk of intertrochanteric/femoral neck fractures after one year of high compliance with bisphosphonate therapy, and which remained reduced for the duration of therapy; however within this research, there is increased risk of subtrochanteric/femoral shaft fragility fracture from year two, culminating at greatest risk at year five [200]. In similar studies, there is more than double the risk of atypical femoral fractures linked with consistent bisphosphonate use of five years or longer [75, 203]. An association between atypical femoral fracture and bisphosphonate duration has been suggested by the ASBMR taskforce [198, 199]. There was a reported increase from 2 per 100,000 people on treatment per year following two years of therapy, up to 78 cases per 100,000 people following eight years of bisphosphonate use. There is a documented reduction in atypical femoral fracture risk of around 70% per year on cessation of therapy, supporting the theory that resorption and remodelling of bone at sites of microcracks allows damage repair in the absence of antiresorptive agents [207].

There are several theories on the causes of atypical femoral fracture, based on artificially lowered bone turnover allowing for greater levels of microdamage

accumulation over time [208]. It is speculated that bisphosphonate accumulation at the site of microdamage may inhibit the repair of micro cracks, allowing propagation of stress fracture. It may also be the case that hypermineralisation of the bone coupled with reduced heterogeneity of the bone lead to changes in collagen structure resulting in brittleness of the bone [198].

Bisphosphonates have a high affinity for calcium, and they concentrate in the body at sites of active bone turnover. As fractures heal by bone remodelling, bisphosphonate therapy may delay the healing process, allowing the further development of fractures [207, 209]. Incomplete fractures are further complicated in the healing process by the fact that the microcrack is affected by the slightest of strains and therefore healing is disrupted regularly at the fracture site [204]. This presents a weakness in the bone structure, requiring minimal trauma to cause a complete fracture [3]. A further speculative explanation is that bisphosphonates in circulation will preferentially bind to a fresh fracture site, inhibiting the remodelling process and allowing microcracks to grow rather than diminish, with the ultimate consequence being a complete stress fracture [207]. The risk of atypical femoral fracture appears to be linked to nitrogen containing bisphosphonates as mentioned previously [210].

Atypical femoral fractures present as pain in the affected limb, with little or no trauma, but may be preceded by pain in the groin or thigh of the affected limb [97, 98]. Fractures tend to occur prior to a fall, and there may be little visible outward change in the limb, in contrast to a conventional hip fracture. Research indicates AFF is more likely to happen at a younger age than hip fractures: 70.6 years in Caucasian women, 66.4 years in Asian women [32], in comparison to 77 years for typical hip fracture [211]. One study found 5.9 AFFs per 100,000

person-years in patients exposed to bisphosphonate drugs [212], in contrast to finding 1 AFF per 100,000 person-years in bisphosphonate-naïve patients [213]. These fractures will occur at or below the level of subtrochanteric fracture line indicated in figure 2.1.

There is a general acceptance that intramedullary nailing is the preferred fixation option for complete AFFs, as they provide greater stability at the fracture site [214]. One study demonstrated surgical outcomes of AFF nailing can still be poor, with delayed healing and requirements for revision surgery [103], while another reported no failings of femoral nailing, with the only adverse effect being bone comminution during surgery [215]. Surgical fixation also reduces pressure being placed on the contralateral femur, reducing risk of contralateral fracture, which has been identified in anything from 38-69% of patients with AFF [201, 203]. It has also been identified that there is variation not only between hospital trusts, but between hospitals and surgeons on whether surgical fixation should be considered sooner rather than later, especially in the case of incomplete AFF in the context of contralateral complete AFF. Some studies report a lower success rate in union of the bone in cases of conservative management, with patients taking longer to return to normal activity levels [4]. It is suggested that incomplete AFFs can be managed conservatively, at least in the initial eight to 12 weeks following diagnosis. If no healing is demonstrated, then nailing should be considered in conjunction with the wishes of the patient, with a view to avoidance of complete AFF [5].

Data suggests that the rise in subtrochanteric fractures is more or less parallel with the rise in the rate of prescribing of bisphosphonate drugs, and that the risk

of atypical femoral fracture is decreased on the cessation of bisphosphonate medication by 70% per year [209]. However, it was demonstrated that there was a 30% reduction in risk of hip fracture and no increased risk of femoral shaft fracture when Alendronate was taken as prescribed over a period of ten years [51]. It is universally agreed within the published literature that further research into the causal factors for atypical femoral fractures is required. Many areas such as medication use, hormone imbalance, autoimmune disease and ethnicity have been researched as individual subjects of interest with regard to atypical femoral fractures and osteoporosis, but not as a whole. Several papers speculate that atypical femoral fracture risk is greatest in females over the age of 70 years, with a low BMD, Asian ethnicity, previous vertebral fracture, high bone turnover markers, glucocorticoid therapy and low Vitamin D status [31, 32, 75, 153, 200] . There is evidence of increased risk of AFF with Asian ethnicity at a younger age [32, 75, 76, 97, 201], BMI in range 18.5-24.9, and prior exposure to bisphosphonate therapy [75]. Findings of one study indicated that patients with AFF were less likely than the general population to have diabetes mellitus, while in contrast another found that diabetes was more common in patients with beaking [99]. This study was based on patients taking bisphosphonate drugs and glucocorticoids and this may have had an influence on these findings, as glucocorticoids are known to induce diabetes mellitus in some patients with long term use [216]. One study found that all AFF sufferers were female, with 75% of those taking bisphosphonate drugs, mean age of 72 years, accounting for just under 3% of all hip fractures studies [211].

Other issues related to long term bisphosphonate use can be ascribed to the length of treatment plan; osteonecrosis of the jaw, atypical femoral fracture and

damage to bone microarchitecture due to over suppression of bone turnover. Osteonecrosis of the jaw (ONJ) is diagnosed where the bone of the jaw is exposed following an extraction or other oral surgery and has not healed within 8 weeks. This is estimated to affect between 1-12% of patients using high dose bisphosphonate drugs as part of cancer treatment [217]. Identification of ONJ in patients taking antiresorptive medications is substantially lower, by factors of 100-250 times reduced, and only when dental extractions have taken place [218]. Signs and symptoms include pain in the affected area, loose tooth, swelling and ulceration of the affected area [217], although it is unknown specifically in which order these occur [219].

### 2.3.1 Treatment benefits and risks.

The benefits of osteoporosis drug treatments include; reduced risk of fracture [51], repair of bone, increase in bone density with improvements identified in BMD within 6-12 months of initiation of therapy [220]. Modest increases in BMD of around 4% are associated with bisphosphonate use, alongside a 30-40% reduction in fracture risk [221], with one study estimating a fracture risk reduction of 26% after one year of complaint bisphosphonate therapy [222]. Strict compliance with bone strengthening medications give optimum fracture risk reduction, but these medications also confer additional risk of significant associated side effects of taking these drugs, of concern to many patients is the risk of osteonecrosis of the jaw and also atypical femoral fracture. Where there is patient concern regarding atypical femoral fracture, it may provide reassurance to know there was a relatively simple monitoring process in place which can be combined with the routine DXA scanning regime already in place to monitor bone density.

## 2.4 Current uses of DXA in management of osteoporosis.

Bone mineral density measurements of the hip and lumbar spine are considered gold standard, providing sufficient data to evaluate the bone density. Scanning the proximal hip area takes around 45 seconds, with the addition of distal femur scan increasing the scan time by around 60 seconds, allowing an assessment of the femoral cortex to be made at the same as BMD acquisition. Minimal change in positioning technique is required to perform an extended femur scan, and the ability to compare newly acquired images with previous scans is unchanged. The additional time taken and radiation dose is minimal, as demonstrated in table 2.2.

Table 2.2 Additional time and radiation exposure of extended femur DXA scan.

| Projection (single femur) | Time taken (seconds) | Radiation exposure ($\mu Gy$) |
|---|---|---|
| Proximal femur | 45 | 37.0 |
| Distal femur | 57 | 18.5 |
| Total extended femur | 102 | 55.5 |


Figure 2.2 Extended femur DXA scan image.

Scanning of the extended femur would not occur in patients under the age of 20 years, as the femoral epiphyses may not have fused prior to this age rendering any result unreliable. Patients with previous hip fracture, pinning or

replacement would not be eligible for scanning of the extended femur and hip as reliable measurements cannot be post fracture or following insertion of prosthesis. Similarly, lumbar spine scanning and analysis is affected by the insertion of any structural metalwork, vertebral fractures and any other overlying artefacts/calcifications such as aortic calcification. Both extended femur and spine scans are undertaken with the patient lying on the scanner, and using the positioning devices supplied with the scanner. A typical extended femur scan is shown in figure 2.2.

The primary management of osteoporosis uses bisphosphonate drugs to slowly rebuild the internal structure of the bone matrix, to add strength and reduce the incidence of fracture. This has been demonstrated to slow age related bone loss and also stabilises the bone microarchitecture. It has been demonstrated that up to 30% of the benefit of bisphosphonates are due to anti fracture effect and increase in BMD, the remaining benefit is due to improvement of the microarchitecture within the bone structure [223]. Such benefits can be quantified using serial DXA scans to measure increases in BMD, but do not give indication of the quality of the bone structure.

As osteoclast activity is inhibited by bisphosphonate drugs, concerns have been raised regarding the over suppression of bone remodelling, resulting in the body having an impaired ability to repair micro fractures associated with stress fractures, specifically atypical femoral fractures. In some circles it is believed that the reduced bone turnover makes the cortical bone brittle and easier to fracture, while others believe the cause to be the inability of stress fractures to

heal as there is constant movement at the site of the micro fracture [208]. Though uncommon, these fractures are typically seen in patients with prolonged bisphosphonate exposure and higher treatment compliance levels, however there have been rare cases demonstrated in patients with no bisphosphonate exposure [211].

DXA scanning is considered as the gold standard test for the formal measurement of bone mineral density, and uses calculations based on two separate x-ray beams of differing energies to measure attenuation of soft tissue and bone. This system measures bone mineral content from the regions scanned, and a value for bone mineral density calculated by dividing the bone mineral content by the area measured. From this, an evaluation of BMD can be made; measurement of BMD of one or both hips and lumbar spine is standard clinical practice. Extended scanning of the femur may present an ideal opportunity to assess the cortex of the femur while concurrently evaluating BMD. Full femoral measurement is taken at time of bone mineral density scan, with no detriment to BMD measurements [224], minimal additional radiation exposure and no extended appointment time required. This scan can aid identification of any increased area of cortical width caused by localised periosteal reaction, which may be an early indication of a future fracture site. In some cases this reaction, or peak, may represent an old injury, a prominent muscle insertion point or other irregularity unrelated to atypical femoral fracture or beaking. Using the software alongside visual analysis of the femoral cortex and with identification of prodromal pain, it may be possible to identify prefractures earlier than relying on prodromal symptoms alone. The software supplied by GE provides a quantitative measurement of beaking along the length of the visualised femoral shaft, measuring focal thickening of the lateral

cortex. Over serial scan measurements a beaking profile is created, allowing graphical demonstration of any irregularities.

This function is also useful on initial scan, as peaks may be identified at this point where present, with no requirement to wait for further scan images to identify irregularities. The extended femur scan takes around 57 seconds longer to acquire, with an additional radiation dose of 0.18μSv per femur, the dose and time measurements are very similar to those quoted in the 2017 works of Van De Laarschot and colleagues [225]. It is accepted that there is a paucity of data as to whether these cortical lesions accurately predict the future development of AFF, nor has the timescale involved in their development been confirmed [226]. It is also largely unknown if some of these lesions spontaneously resolve, or are associated with other factors. There is very limited evidence on the use of extended femur scanning software on bisphosphonate-naive individuals, previous focus has been on establishing links between bisphosphonate use and atypical femoral fractures [15, 75, 200]. The main recommendation has been to use x-ray as a means of monitoring the cortex of the femur for thickening/beaking [97, 227].

This body of work adds to the research already undertaken in analysis of the opportunistic identification of AFF at the time of routine DXA scanning using extended femur scanning and specialist software on a clinical population. As the prevalence of AFF is low, there is a requirement for research to be conducted in exploration of cost effectiveness and clinical utility of this measurement technique for use within the NHS.

## 2.5 Summary.

In the following section the methods used are considered in detail in order to extend the knowledge of atypical femoral fractures and DXA scanning, including a comprehensive review of the relevant literature, based on the objectives and questions below.

### 2.5.1 Objectives:

1) To prospectively evaluate the use of GE Lunar extended femur DXA scanning software in a routine clinical environment.
2) To investigate the incidence rate and risk factors of iAFF/AFF within NHS Grampian and compare with those quoted in a review of the published literature.

### 2.5.2 Research questions:

1) What is the clinical utility of this measurement technique in conjunction with routine DXA scanning?
2) Is the reproducibility of the hip BMD measurement affected by the software?
3) Are the software measurements reliable and reproducible in a patient population?
4) What is the incidence of iAFF and AFF in a clinical population?

# 3 Method section.

This section details the methodology and methods used to undertake the data collection (page 79), analysis of ten year data on hip fractures (page 81), various audits and service evaluation (page 83), and a small in-vivo precision study (page 89). All of which were undertaken as part of this study to assess the extended femur scan software in clinical practice.

## 3.1 Approvals process.

This section outlines the processes required to gain approvals for each audit and in-vivo precision study, the relevant permissions and related documents are appendices at the end of the document.

### 3.1.1 Phase 1 approvals.

The following elements of the overarching study were categroised as a service evaluation by research and development (R&D) department of Grampian health board: femur scan positioning audit, scan technical analysis audit, visual assessment of femoral cortex for peaks, automated software analysis of peaks, patient demographics and data collection for comparative use, incidence of AFF in NHS Grampian 2008 – 2018.

A service evaluation was carried out to evaluate current practices as part of routine clinical care, with extended femur scanning embedded in routine clinical practice within NHS Grampian in September 2018. The outcomes of service evaluations are used to improve patient care pathways through objective

assessment and analysis of practice, and using the results to make evidence based changes to practice where appropriate [228].

The study proposal was registered with NHS Grampian clinical effectiveness department and study number 4194 was issued. Caldicott guardian approval was obtained to access patient information and images for the purposes of the study. Audit approval was also obtained from NHS Grampian for relevant parts of the study detailed in section 9.1 – 9.7.

### 3.1.2 Phase 2 approval – In-vivo precision study.

A study involving extended femur scanning of extended femur bench phantoms using the new version 17.0 scan software has been conducted by GE, therefore it was decided to conduct an in-vivo precision study in order establish whether any measurement differences were found in humans. The precision study element required permissions from the Health Research Authority, with the University of Exeter acting as sponsors. The study was registered with the Integrated Research Advisory Service (IRAS), study application number 259999, North of Scotland Research reference 19/NS/0183, sponsorship number 1819/42 (University of Exeter). A submission was made for ethical approval for precision study through the Integrated Research Application System (IRAS) and the Health Research Authority, and approval was granted by NHS research ethics committee in December 2019. This was necessary as additional scans and radiation exposures were made to study participants in addition to routine clinical care, for a study population of 30 patients. Each consenting participant had duplicate extended femur scans at the routine scan appointment. All supporting documents and permissions can be found in

appendix 9.1 – 9.7, including patient information sheet, covering letter, consent from and study protocol.

### 3.2 Outline of activity.

From September 2018, the use of GE Lunar extended femur scan software, designed to provide early identification of AFF was embedded within routine clinical practice on all DXA scanners within NHS Grampian. This software allows the visualisation and assessment of the full length of the femur, with automated software measurement of the lateral femoral cortex. This was designed to allow identification of cortical defects including the thickening of the cortex, and incomplete atypical femoral fractures (iAFF), integrated with BMD measurement at the proximal femur. As the software was new to the service, an evaluation was required to assess its clinical use in relation to AFF and iAFF, and as part of that evaluation an in-vivo precision precision study was conducted. An in-vivo precision study was undertaken in order establish whether any measurement differences were found in humans, in contrast to the results of the phantom measurements found by GE using the same software. There is inherent inhomogeneity in human tissue, and the act of repositioning between scans can mean a small amount of change in how the tissue lies during scanning. This can have the effect of altering the BMD results, which is the primary measurement obtained from DXA scanning. In order for serial scans to be comparable, reproducible patient positioning is essential, to ensure best comparison of BMD. This ensures any change in BMD is real, rather than something engineered by changes in equipment, positioning or staff. Post scanning, there is a requirement to audit and assess the quality of scans, both

in technical terms and in patient positioning, to ensure no detriment to measurements acquired or to patient care from the implementation of the extended femur scan. These images and figures are the basis of the clinical report, and are also used to evaluate the femoral cortex for signs of iAFF or other abnormalities. It is critical to the identification and management of iAFF from extended femur scans that all staff are using a standardised criteria to assess scans, and that software automated analysis of peaks does not alter should any scan reprocessing be required post-scan.

This led to the formulation of a series of audits, data collection and an in-vivo precision study, as listed below, in order to establish the usability and stability of the scan software in a clinical environment, and to establish the scale of AFF within NHS Grampian. The timeline displayed in figure 3.1 gives an overview of the work undertaken within this study;

- Prospective data collection and patient demographics of all patients scanned within the department over a six month period for comparative use
- Retrospective health intelligence data on femur fractures and the incidence of AFF in NHS Grampian 2008 – 2018
- Femur scan positioning audit
- Scan technical analysis audit
- Visual assessment of femoral cortex for peaks
- Automated software analysis of peaks
- In-vivo precision study

Routine quality assurance and control were performed throughout the process as normal, alongside cross calibration of all scanners using a spine phantom as per good clinical practice, details of which are in appendix 9.8.

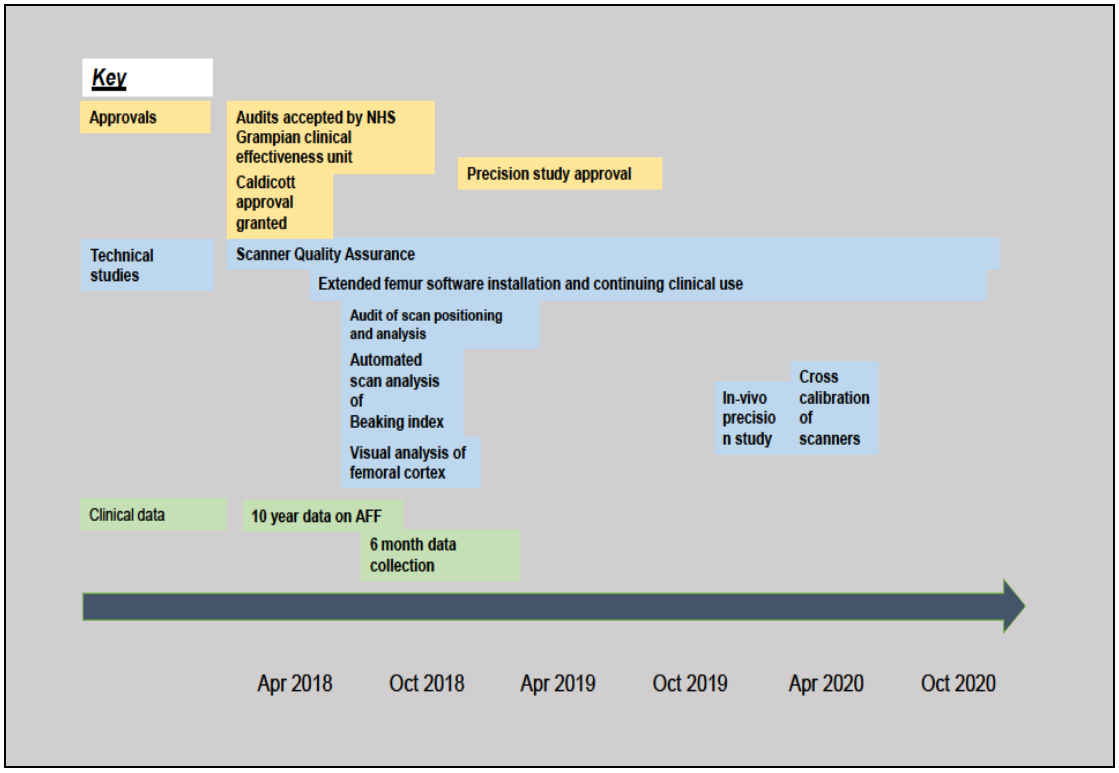



Figure 3.1 Visual representation of permissions, audit and study timeline.

### 3.3 Data collection.

Following the installation of extended femur scanning software, patient demographic data was collected on all patients attending for DXA scanning over a period of 6 months between Sept 2018-March 2019. All staff were briefed in data collection requirements. Caldicott approval was granted for patient identifiable information to be collected and used. Data were gathered from all

scanners and sites – including age, sex, ethnicity, height and weight alongside self-reported exposure to the following: bisphosphonate/bone strengthening drugs, hormone replacement therapy (HRT), glucocorticoid tablets, smoking, alcohol, anti-oestrogens, anti-androgens, proton pump inhibitors (PPI), thyroxine, selective serotonin reuptake inhibitors (SSRIs), peaks >1mm as measured by software and groin/thigh pain. These data will be used to give an overview of the patient demographics routinely scanned within the department and to offer comparative data for other sections of the study. A Microsoft Excel (2013) spreadsheet was created and paper copies of this were positioned at each scanner area for completion by all operators following every patient appointment. Instructions were reiterated via email on how to complete the data, a blank spreadsheet and instructions for completion are found in appendix 9.9. Data was collected on a yes/no basis for various medications, recorded as a tick or cross, and smoking was described as past, present or no. All staff participated in the data collection, and each page of the spreadsheet was returned to the radiographers' office for input to an electronic version of the same spreadsheet. From this information, scan data was downloaded electronically from the scan database to the Excel spreadsheet, then matched with the patient data based on Community Health Index (CHI) number, and combined using an Excel macro based on patient CHI number. A selection of randomly chosen patient data was then cross checked with date of birth to ensure accurate transcription and combination of data.

## 3.4 Retrospective ten year data on the incidence of atypical femoral fractures within NHS Grampian.

Retrospective health intelligence data was obtained of all patients suffering a femur fracture within NHS Grampian. This was collated using ICD coding for all patients over the age of 50 years over a ten year period from 2008 to 2018 (n.7102). Local Caldicott approval was obtained, and registered with NHS Grampian clinical effectiveness unit as a clinical audit.

Collated to an Excel spreadsheet were fractures S722 subtrochanteric, S723 shaft of femur, S724 lower end of femur, S728 other parts of femur, S729 femur part unspecified. Fractures of the neck of femur S720, pertrochanteric S 721 and multiple fractures of femur S727 were excluded from analysis as they do not meet the ASBMR criteria which specifies that to be considered as an AFF, the fracture must be located along the endosteal femoral cortex from anywhere distal to the lesser trochanter but to proximal to the supracondylar flare [198]. Once these patients had been excluded from analysis, a total of 564 patients required adjudication, which was carried out by a specialist radiographer and a fifth year medical student using radiographic images held within the Picture Archiving and Communication System (PACS). All patients with subtrochanteric fractures were investigated (n. 192) using medical records and radiological imaging, including previous DXA scans where available.

Those patients with shaft of femur fracture (n. 131), fracture of lower end of femur (n. 173), fracture of other parts of femur (n. 28), fracture of femur – part unspecified (n.40) were investigated using radiological imaging primarily, and those fractures not meeting with the criteria laid down by the ASBMR task force in table 3.1 [199] were excluded. Any patient with radiological imaging meeting

these criteria were investigated thoroughly using medical records and, where available, previous DXA scans.

Fractures without radiological features in keeping with AFF were excluded from further investigation. Electronic patient notes were checked for specific mention of AFF in orthopaedic notes or any other correspondence. From this data, a small pool of patients were identified for further detailed investigation of records, medical history and background to build a profile of individuals affected by AFF. If no mention was found in patient records of AFF, the patient was excluded from further review, which may have inadvertently excluded some patients. There were a a number of images sent to an orthopaedic surgeon for adjudication, where there was a dispute between two viewers, with the results unavailable at the time of writing.

Table 3.1 Definition of atypical femoral fracture (major and minor criteria) adapted from ASBMR taskforce revised case definition (2013). [199]

| At least four of five major features must be present:* | Minor features are not required for diagnosis |
|---|---|
| 1. The fracture is associated with minimal or no trauma, as in a fall from a standing height or less. | Generalised increase in cortical thickness of the femoral diaphysis. |
| 2. The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur. | Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh. |
| 3. Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex. | Bilateral incomplete or complete femoral diaphysis fractures. |
| 4. The fracture is noncomminuted or minimally comminuted. | Delayed fracture healing. |
| 5. Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”). | |

AFF – atypical femoral fracture, ASBMR – American Society for Bone and Mineral Research.

*Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumours and miscellaneous bone diseases (e.g., Paget's disease, fibrous dysplasia).

### 3.5 Femur scan positioning and technical analysis audit.

This service evaluation was undertaken to assess individual patient positioning and the technical quality and evaluation of the scans by all operators within the department. Caldicott approval for given to access patient identifiable information in this context, appendix 9.7. The audit was undertaken of 30 random femur scans from all specialist radiographers employed within the service (n. 5) and scanners (n. 4) used within the department. Scans were selected which took place between 01.12.2018 and 31.03.2019, no scans were excluded. The analysis template and criteria are attached, appendix 9.10.

All scanner operators are qualified diagnostic radiographers, registered with the Health Care and Professions Council (HCPC), and trained to scan in line with the GE Lunar DXA scanning user manual. All scan analysis techniques and technical criteria are taken from the same. All operators have been trained and certified by the National Osteoporosis Society in bone densitometry, a template of the training record used in the department is attached in appendix 9.11.

Extended femur scans were assessed using a standardised assessment template, adapted from GE Lunar scan manual and a DXA scan technique audit tool already in use within the department. Scans were assessed on the accuracy of the bone mapping, indicated by the yellow lines around the bone, ensuring no ischium or greater trochanter mapped as bone in the measurement of the femoral neck, within the blue rectangle at the femoral neck.

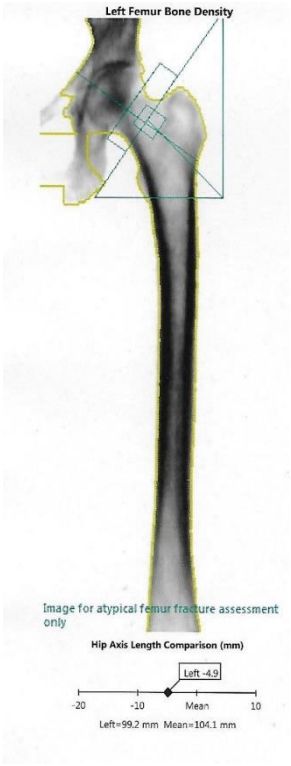



Figure 3.2 Extended femur DXA scan, representative of a technically high quality scan with appropriately positioned regions of interest.

Assessment was also made of region of interest placement, where the femoral neck region of interest box should have four corners in soft tissue, the mid femur axis line bisects the femoral head correctly, running through the centre of the fovea capita, which allows positioning of the femur neck box perpendicular to the femoral neck. Figure 3.2 is representative of a high quality scan with

excellent technical accuracy. No details were available of any difficulty with patient positioning, habitus or co-operation, which can all affect scan quality.

### 3.6 Visual assessment of extended femur scans for beaking.

This audit comprised the analysis and assessment by four experienced DXA scan viewers of 30 preselected individual femur scans for visual assessment of beaking. Scan images were selected at random from scans acquired across all scanners and operators, between September 2018 and January 2019. These were saved to a folder on a desktop computer for ease of access for all users, and to ensure users access scans in the same manner. All assessments were carried out using the same workstation using the same generic login to minimise differences in screen resolution, windowing and ambient light. The assessments were carried out independently, as convenient. All scans were single femur, anonymised and saved with file numbers to ensure no identifiable patient data were presented, no patient history was provided, Caldicott approval was granted for the use of patient data.

The viewers visually assessed the lateral cortex of the femur on each scan image individually from the file provided. An opinion was then recorded on whether any signs of lateral cortical thickening/beaking were visible, and record as positive/negative on a spreadsheet. This was based on the image alone, and without viewing the AFF tab of the scan software, or consulting with colleagues, avoiding external influence.

Beaking is classified as an area of diffuse periosteal reaction or thickening, occurring on the lateral cortex of the shaft of femur, which may be an initiation point for an atypical femoral fracture, a type of stress fracture. The area of cortical thickening is known as a beak, and the process of thickening is known as beaking. Any area of thickening is measured in millimeters (mm) to one decimal place by the scan software, and a coloured arrow automatically placed at the level of any peak measuring ≥1mm alerts the user to level of the irregularity. The beaking index is measured as the distance from the inner cortical wall to the edge of the beak, minus the cortical wall measurement in areas above and below the beak – all measurements are made in millimetres (mm). A pictorial representation of the measurement points are shown on figure 3.5. The suggested threshold from GE Lunar for flagging beaking is 1mm [229].

The scan image in figure 3.3 gives an indication of a scan exhibiting beaking as measured by the scan software, which could be considered to be a false positive, as the cortex appears smooth and congruent. Figure 3.4 demonstrates a true positive beak on DXA scanning, showing a peak on the lateral femoral cortex mid shaft of femur.


Figure 3.3 Software manufactured false positive beaking at distal femur on extended femur DXA scan.

### 3.7 Scan analysis – software automatic beaking index measurement.

Scan analysis and re-analysis was carried out in January 2019, examining 30 random single extended femur scans in triplicate, acquired between September 2018 and January 2019. From this, the beaking index figure was recorded to one decimal place, as calculated by the scan software. This was performed on 3 separate dates, where the same scans were opened and automatically reanalysed using the scan software by the same specialist radiographer, and the measurements recorded. No adjustments were made to any area of the scan, which were selected from all operators and scanners within the department, with no exclusions or patient history given.

The beaking index is a quantitative measurement automatically acquired by the scan software, measuring the increase in cortical width of any localised periosteal reaction, in mm. The threshold measurement for this is 1mm, anything greater than 1mm will be automatically flagged by the scanning software to the operator by means of a coloured arrow adjacent to the area concerned. This is calculated by measuring the lateral cortex of the femur at the point of beaking in mm, then subtracting the thickness of the cortical wall where considered normal above and below the beaking area.

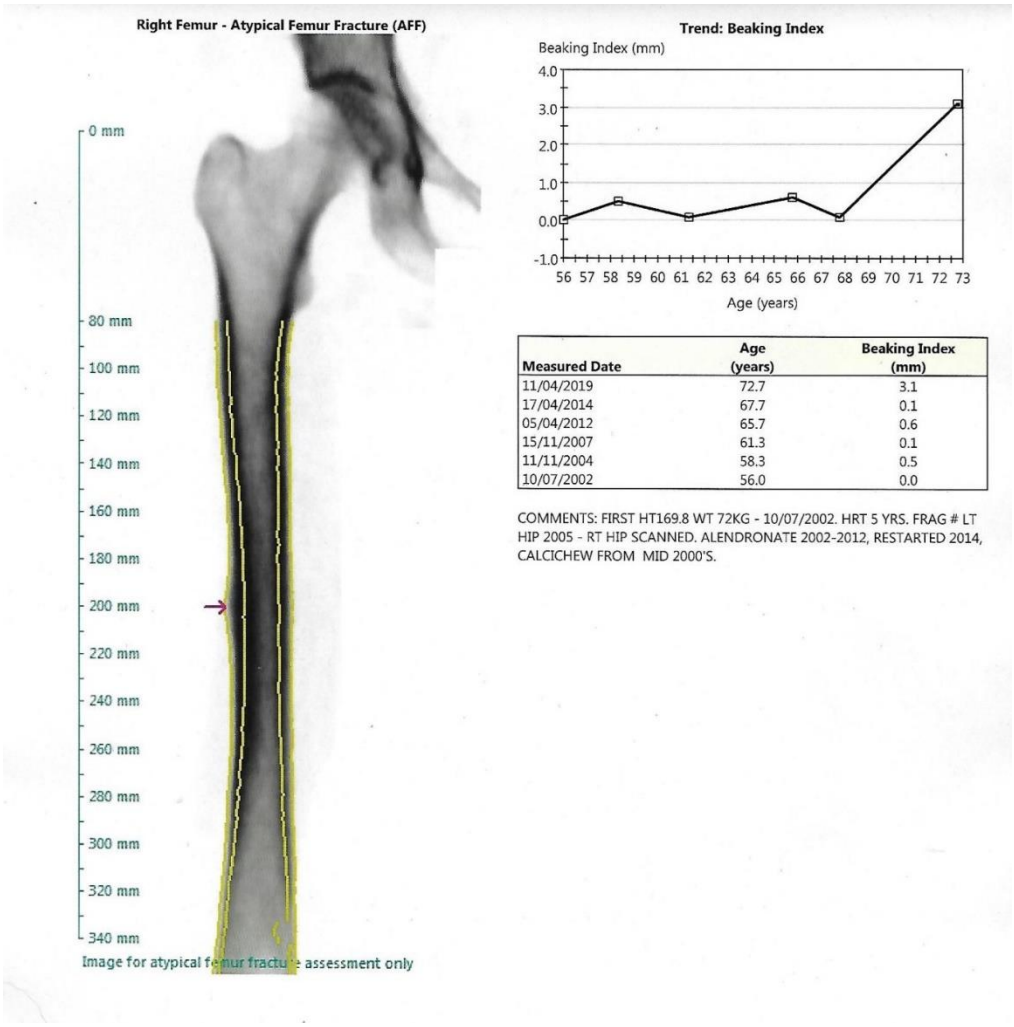



Figure 3.4 True positive beaking as seen on an extended femur DXA scan image.

## 3.8 Precision study.

This section outlines the in-vivo precision study undertaken using DXA extended femur scanning software.

### 3.8.1 Aim.

The aim of the in-vivo precision study was to investigate the operator precision error of extended femur scans on a static scanner. This was conducted by undertaking in-vivo precision study on patients >20 years routinely attending the Grampian Osteoporosis Service at Ashgrove House, Aberdeen Royal Infirmary, for DXA scan. All scans were undertaken on the same scanner by the same specialist radiographer.

When comparing BMD measurements over time in the same individual it is important to distinguish between a true change in the measurement and inherent precision error related to variability in the measurement procedure [230]. Scanner manufacturers General Electric (GE) Lunar suggest that accuracy and precision error of the measurements taken from the outer edge of the femur (thigh bone) during extended femur scanning software are within an error margin of 0.5mm, using simulated beaks contained within phantom. No DXA measurements have been performed by GE on a clinical population, using real patients. Correct and reproducible positioning of patients is necessary to ensure continuity and accurate comparison of measurements, incorrect positioning can result in measurement differences of greater than +/- 0.5mm [229]. This is new software and it is not yet known how reproducible these measurements are in a clinical population, or indeed any effect this may have

on BMD measurements, and no published evidence has been found to suggest anything similar to this study has been undertaken on a patient population.

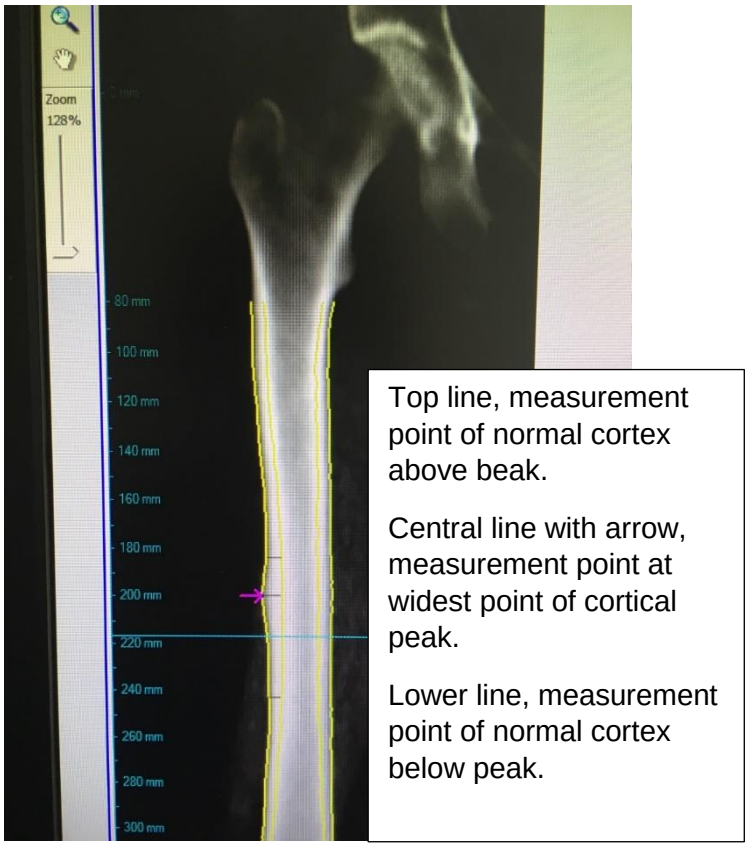



Figure 3.5 Extended femur scan image with measurement points identified.

By investigating the precision error, or reproducibility, in a patient population typical of those referred to the service, it can be ascertained that the measurements obtained are true. This was done by measuring the thickness of the outer edge of the cortex of the femur, used in routine clinical practice within the department. This will assist in ensuring the best care for all patients and inform medical imaging pathways in future.

### 3.8.2 Inclusion/exclusion criteria for precision study.

The request for DXA scanning was made by the referring physician and vetted in the usual way as per local referral guidelines for DXA scanning and IR(ME)R Regulations. All patients >20 years routinely attending the Grampian Osteoporosis Service at Ashgrove House, Aberdeen Royal Infirmary, for DXA scan were considered eligible for inclusion.

Exclusion criteria were as follows: Patients <20 years of age, patients unable to give consent, patients who have had bilateral hip surgery, patients who are pregnant. Any patients under the age of 20 years were automatically allocated to have proximal hip scan only, as epiphyseal fusion of the proximal femur is not guaranteed to have occurred prior to this. Also excluded were patients with bilateral hip replacement/pinning as no BMD measurements were obtainable, and pregnant patients who would not be scanned in routine clinical practice.

### 3.8.3 Precision study recruitment.

Recruitment was planned of 30 participants, with study information sent to around 75 participants, in the assumption that approximately 50% of those would consent to participate [231]. It is suggested that 30 participants be scanned to obtain statistically valid results [232, 233]. It is a recommendation of the International Society for Clinical Densitometry (ISCD) that 30 degrees of freedom be used to assess short term precision in DXA measurement, scanning 30 patients, representative of the typical scan population within the department, in duplicate [230]. This posed least inconvenience for participants as they would not be required to return for any further scans or interventions.

Routine clinical care involved one DXA scan (bilateral extended femur and lumbar spine), performed on a GE Lunar Prodigy DXA scanner with version 17.0 software (GE Healthcare, Bedford, UK). Each study patient received additional scans of both extended femur, plus standard clinical care. Appointment times were 30 minutes long with one visit per participant and no further follow up except standard clinical care. All eligible patients weresent an invitation letter to participate in the study and a participant information sheet in addition to their standard clinic appointment letter. These were routinely sent out in advance.

On the day of the appointment, potential participants were approached by the specialist radiographer undertaking the scan and asked if they have read and understood the information sent out. They were then asked if they would be willing to participate. Any questions or queries were discussed. If the patient was happy to participate, written consent was obtained, a copy of the completed consent form was given to the patient to take away with them.

### 3.8.4 Patient pathway.

All participants had their personal details checked with departmental records, discussed the standard osteoporosis department questionnaire, and measurements of height in centimetres (cm) to the nearest 0.001cm using a Holtain stadiometer (Crymych, Dyfed, UK) and weight in kilograms (kg) to nearest 0.1kg using Marsden professional digital scales (Rotherham, UK) are taken as part of routine care. Body mass index was calculated as weight(kg)/height($m^2$), automatically calculated by the scan software. Patient

preparation followed standard clinical care, with removal of underwired bras, jeans and any clothing with metal studs/zips/decoration which may have interfered with scan measurements.

The participant was then asked to lie centrally on the scanner bed, and scans were taken of each extended femur individually, then the lower spine scanned (three individual scans) as per standard practice. For the extended femur scans, a rigid plastic positioner was used to position the legs for scanning. This was supplied with the scanner, fitted with Velcro to support the feet, allowing the patient to relax the leg muscles. The purpose of this was to rotate and abduct the femur, and used as standard to ensure reproducible images and results. The scanner arm passed up and down the length of the scan table, over the body acquiring images as it did so. The images acquired were used initially to ascertain straightness and centralisation of the femur, and alterations in positioning were made until the femur was straight and central in the scanner field of view.

After this process, the participant wasasked to rise from the scanner bed, and then lie back down, mimicking a patient returning for a second scan and considered best practice for short term precision scans. A further scan of each extended femur was taken (two additional scans) in the same manner as the first, using the foot positioner. Following this appointment, the participant was able to access a clinical diagnosis via the referring clinician as per standard clinical protocol.

3.8.5 Scan analysis.

All scans were analysed by the operator, following the departmental protocol. As part of the extended femur scan analysis, the regions of interest should be considered as follows: acetabulum fully visualised, adequate visualisation above the greater trochanter, recommended as two to three sweeps. All four corners of the femoral neck box should be located in soft tissue, no ischium mapped as bone in femoral neck box and the mid femoral line should bisect the femoral head, running from the greater trochanter through the fovea capita to the pelvic brim. The neck box should be perpendicular to the femoral shaft. If there are any changes made to the size, position or angulation of the neck of femur box, the search button should be used to return the box to the point of lowest BMD. The femur should be central, straight and vertical in the field of view, at the proximal end the lesser trochanter should be minimised as far as patient habitus allows; at the distal end there should be no patella or supracondylar flare in the scan field.

## 3.9 Departmental scan protocol.

Standard departmental clinical scanning protocol consists of bilateral extended femur scans and lumbar spine, with the addition of lateral vertebral assessment scan at the discretion of the operator if clinically indicated. Exceptions are hip surgery, and the inability to transfer to the scan table independently. In the case of limited mobility and inability to transfer, a forearm scan can be performed.

Diagnostic radiographers must be registered with the Health and Care professions council (HCPC), all staff acting as operators are diagnostic

radiographers who have completed in-house bone densitometry training as well as completing the Royal Osteoporosis Society (formerly the National Osteoporosis Society) training course and subsequent examination in bone densitometry. Standard operating procedures (SOP) are written for each scan acquisition process, and new staff read, follow and are supervised by an experienced staff member until both parties feel that scan acquisition and analysis is consistently of a high standard. This ensures all staff are trained consistently to the same high standards. The scan acquisition protocol is summarised below, the full SOP is attached in appendix 9.12, and training record template in appendix 9.11. Following the implementation of the version 17.0 software upgrade, a briefing of all staff individually was undertaken by the installation engineer on the use of the new software. The extended femur scanning was the only modification to routine practice, and all staff appeared confident in positioning for and performing the scan.

It is standard clinical protocol to perform PA spine scan and bilateral extended femur scans which cover hip area measurement. Exceptions to extended femur scanning : bilateral hip replacements in situ, previous hip fracture or metal work inserted, even if metal work has subsequently been removed – scan unaffected hip only. It is not considered clinically appropriate to acquire hip scans if the patient is under 20 years of age, as the femoral epiphyses may not be fused until this age.

Scan acquisition standard protocol – extended femur scanning

- Patient details are input and edited correctly to the appropriate DXA scan database.
- Click measure.
- Click dual femur or single femur as appropriate (hip pinned or replaced).
- Click position – scanner will home to foot.
- Patient lies supine on the table centred to the mid line.
- The arms are placed on the patient's chest away from the area to be scanned.
- Ensure that the pelvis is centred in the middle of the scanning field.
- The patient should not be rotated – ASIS of the pelvis must be equidistant from the table-top or as can be reasonably achieved.
- The supplied angled foot support is placed between the patient's feet, abducting the leg to be scanned approximately 15 degrees away from the midline, and internally rotated by around 25°, to rotate the greater trochanter anteriorly and the lesser trochanter posteriorly.
- Knees should be internally rotated and toes should be up – shoes should be kept on.
- Ensure the shaft of femur is straight to allow ease of positioning for follow up scans.
- Using the positioning lights the scanner is centred over the left patella, and the scan ends approximately 30 mm (two sweeps) above the greater trochanter.
- Click Start
- Scan hip – when completed - option to re-measure or save data

- Re-measure if appropriate
- Save
- Scanner automatically moves to scan R femur
- Position laser light appropriately as above
- Scan femur
- Save, Analyse, Save
- Close

If a patient has been scanned before, the previous scans may be accessed by using the 'Settings' facility. This allows previous scan to be viewed simultaneously whilst scanning. The previous scan is essential to enable accurate positioning, the original positioning should be reproduced where possible, this allows superimposing of the original scan over the new scan using the copy feature, which is departmental policy. The regions of interest should not be altered if possible when a patient has been previously scanned, as slight positioning differences may lead to inappropriately positioned to ROI boxes.

### 3.10 Data analysis.

Data analysis was conducted using Microsoft Excel 2013 and IBM SPSS Statistics software (Version 26, IBM, NY, USA). Data were tested for normality and data found to have a Gaussian distribution reported as means and standard deviation, and analysed using parametric methods, data with non–Gaussian distribution reported as median and range, and analysed using non–parametric methods.

Means were calculated using Excel for normally distributed data, in beaking index and cross calibration of DXA scanners. The mean figure was also used to calculate a 95% confidence interval, where upper and lower intervals found by the addition or subtraction of 1.96 respectively from the mean value to give two standard deviations from mean [234]. These data were utilised in the construction of a Bland-Altman plot.

Median calculations were used to analyse data which did not confirm to a Gaussian distribution, such as in the investigation of BMI, using Excel. The standard deviation was calculated using Excel to express variability in the population, and also to measure confidence in statistical results. It is considered that only data outwith two standard deviations is seen as statistically significant [235]. Calculation of BMI was made by the DXA scan software GE Lunar version 17.0 (2017), using raw height and weight data, calculated as weight (kg)/height$^2$ (m).

Extended femur scan precision measurements were used to calculate inter-operator precision error at total hip and femoral neck using the ISCD online advanced precision calculator. The precision measurements of beaking index were calculated using the same program. The precision error is represented as the square root of the mean of the sum of the squares of differences between first and second measurements. The precision parameters, root mean square standard deviation (RMS SD) and root mean square coefficient of variation (RMS CV%) and the resulting least significant change values (LSC) were calculated.

The LSC was calculated by multiplying the precision error RMS CV% by 2.77, and the resultant figure indicates the change in BMD that should be considered

as statistically significant as a true biological change rather than one manufactured by the equipment, operator and changes in patient positioning. If the change in BMD exceeds that of the LSC for the scanner/operator then it can be regarded as a real change in BMD. Accepted figures quoted by the ISCD for 95% least significant change (LSC) for femoral neck is 6.9%, and total hip 5.0% [236].

A Bland-Altman plot was used to display the differences between sets of beaking index measurements, with agreement between measurements and 95% confidence interval calculated.

Cohens Kappa scores were calculated using IBM SPSS Version 26 software (NY USA), to calculate correlation of subjective viewing of extended femur scans. Percentage agreement was also calculated, using Microsoft Excel 2013.

Scan positioning and analysis results were calculated as a percentage frequency, number/total scans*100.

Beaking index analysis and reanalysis was automatically calculated by DXA scan software (Version 17.0, GE Lunar, Bedford, UK).

Sensitivity, a tests ability to identify true positive results, or in this case those patients with iAFF on extended femur scanning, and specificity, a tests ability to correctly identify patients who do not have iAFF on extended femur scanning were calculated using a series of figures based on the following format: a = true positive, b = false positive, c = false negative, d = true negative. The following formulae were used to calculate: Sensitivity = [a/(a+c)]x100, Specificity = [d/(b+d)]x100, Positive predictive value (PPV) = [a/(a+b)]x100, Negative predictive value (NPV) = [d/(c+d)]x100. This allowed the assessment of

probability that a positive (or negative) screening test correctly identified the presence of iAFF on extended femur scanning.

### 3.11 Summary

This section has provided in depth details on the audits and in-vivo precision study methods and data analysis techniques. The following section will cover the service evaluation and data collection findings.

# 4 Service evaluation.

This section will present the demographics of the routine clinical DXA population collected over a period of six months, plus five patients who were found to exhibit true beaking on DXA scans who attended outside this six month window, but within the wider study period. Data on patients with confirmed AFF within NHS Grampian from 2008 to 2018 has also been collated and reviewed to provide an estimation of the incidence of AFF and iAFF in NHS Grampian.

## 4.1 Service evaluation and data collection.

Patient data were collected over 6 months for all patients attending for routine DXA scans within NHS Grampian centres in Aberdeen and Elgin, and satellite sites in Aboyne, Orkney and Shetland, as documented in methods section 2.3. This included six paediatric patients who did not have extended femur scanning performed as the scan software does not allow this prior to age 20 years and clinically this would be inappropriate. In addition, there were 67 patients who did not have extended femur scans performed for a variety of reasons. The participant demographics for all patients attending for scan over the six month period are presented in table 4.1.

Table 4.1 Routine DXA scan patient population descriptive statistics.

| Variable | Population (n. 2588) |
|---|---|
| Sex female/male no. (%) | 2055/533 (79.4/20.6) |
| Age, years, mean (SD) | 66 (12.5) |
| Age range (years) | 3 – 95 |
| Ethnicity (%) | |
| Caucasian (%) | 2384 (92.1) |
| Asian (%) | 12 (0.5) |
| Black (%) | 1 (0.0) |
| Hispanic (%) | 2 (0.1) |
| Not recorded (%) | 188 (7.3) |
| Smoking - past (%) | 1212 (46.8) |
| Smoking – present (%) | 287 (11.10) |
| Alcohol >14 units per week (%) | 185 (7.1) |
| BMI kg/$m^2$ mean (SD) | 27.2 (5.8) |

SD – Standard Deviation

Modifiable risks for osteoporosis are considered as lifestyle choices, as identified in table 4.1, including smoking and alcohol intake. Current smokers accounted for over just over 11% of all patients scanned. Over a third of all individuals scanned had smoked in the past, with a greater number of men being past smokers compared with women. More than 7% of patients scanned indicated they regularly consumed more than 14 units of alcohol per week.

Information on medications known to affect bone metabolism were collected and are outlined in table 4.2.

Table 4.2 Patient medications divided by gender.

| MEDICATIONS | Male n. 533 (%) | Female n. 2055 (%) |
|---|---|---|
| Anti androgen/oestrogen | 7 (1.3) | 139 (6.8) |
| Oral glucocorticoid | 178 (33.4) | 508 (24.7) |
| SSRI | 30 (5.6) | 246 (12) |
| Levothyroxine | 21 (3.9) | 306 (14.9) |
| Proton pump inhibitor | 188 (35.3) | 689 (33.5) |
| Bisphosphonate | 84 (15.8) | 607 (29.5) |
| HRT | 7 (1.3) | 547 (26.6) |

SSRI – selective serotonin reuptake inhibitor; HRT – hormone replacement therapy. Bisphosphonates include alendronic acid, Risedronate, zolendronate, ibandronate, Denosumab and parathyroid hormone.

The use of hormone blocking drugs such as Arimidex and Zoladex was higher in women than men, with just under 7% of women taking of have taken in the past, compared with just over 1% of men. Glucocorticoid use was higher in men than in women, with 33% of men and just under 25% of women taking oral steroids in the past or at the time of scanning. Patients with prescribed medications are displayed in table 4.2, separated by gender.

Hypothyroid treated with Levothyroxine was reported by almost 15% in women, in contrast to less than 4% of men. However, men were found to be more likely to be taking proton pump inhibitor drugs, with 35% of men scanned found to be taking these. The difference between the sexes was not marked however, as over 33% of women were also taking these.

The use of Selective Serotonin Reuptake Inhibitor drugs was also more than double in women at 12% compared to men, at just under 6% of men. However there was almost double the number of women prescribed bisphosphonate drugs compared with men, with almost 30% of women taking or having taken bone strengthening drugs.

From the data gathered, there is no statistically significant difference in the mean age of those displaying peaks on DXA scanning and those who do not. The demographics of patients who exhibited peaks > 1mm on scanning is found in table 4.3, compared with those who did not, separated by gender, alongside medication use. There was no difference between the BMI of men who displayed peaks and those who did not, however female subjects who displayed peaks on scans had around 5% higher BMI than those who did not. Over 27% of patients scanned had a BMI ≥30kg/m². None of the patients scanned over the six month period demonstrated a peak which was considered significant as a true thickening of the lateral cortex of the femur. However, in the 6 months following the data collection period, five patients presented with peaks related to AFF which was confirmed in further imaging. To explore the annual incidence of AFF in the DXA population, the 6 month data were doubled to extrapolate numbers so that the positive predictive value could be calculated. Any data manipulated in this manner will be clearly outlined within this chapter.

Over a quarter of all women scanned had been on HRT either at the time of the scan or in the past. The average BMI for this cohort of patients is just over 27.3 kg/m², the range is between 13.6 and 57.8 kg/m².

The data were divided into bisphosphonate users and non-users for males and females and for those with and those without peaks of greater than 1mm demonstrated on the long femur scans. The numbers are outlined in figure 4.1 and full information on these groups is presented in table 4.3

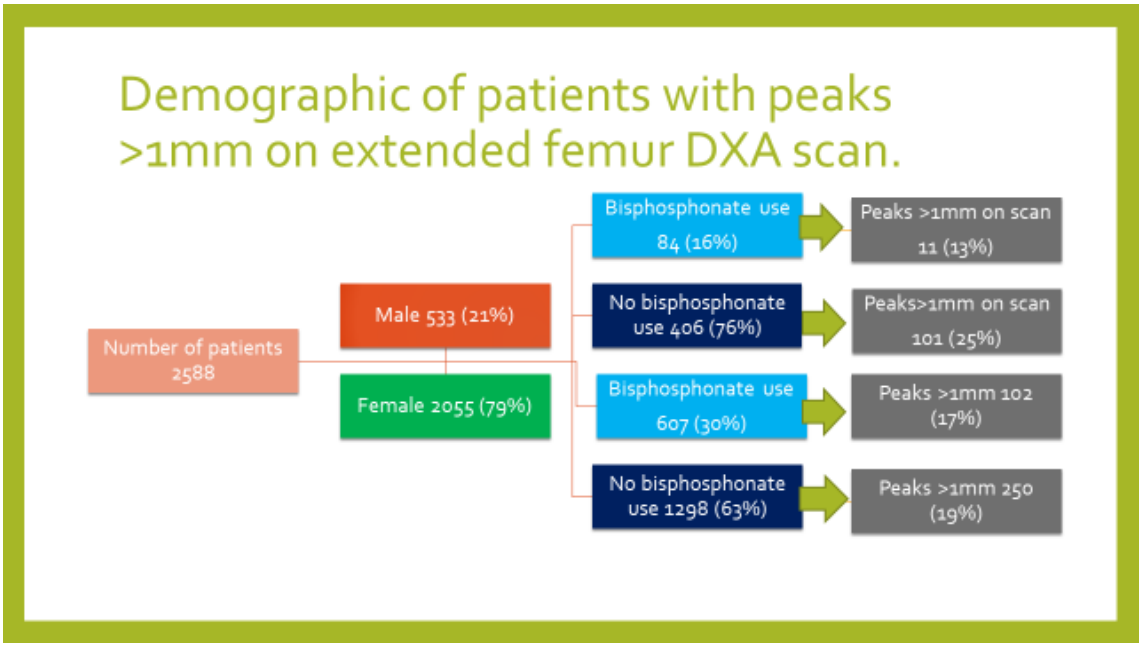



Figure 4.1 Patient characteristics: separated according to peaks on DXA scan and bisphosphonate use.

Of the patients displaying peaks >1mm on DXA scan (n. 464), three quarters of patients were bisphosphonate naïve. Within the male population, 21% of those scanned had peaks measuring >1mm, in comparison to 17% of female patients. Bisphosphonate use (past or present) affected almost 27% of the scan population, no timescale was recorded for the consumption or cessation of these drugs, or self-reported compliance. Figure 4.1 demonstrates the demographic of patients who displayed peaks >1mm on scan software,

separated by gender. The mean age of those displaying peaks on scanning is 66.5 years, identical to those with scans deemed normal.

The results of Chi squared test of association (2x2) indicated a significant association between bisphosphonate use and peaks greater than one millimetre, (Chi square value = 4.568, df = 1, number analysed = 2293, p = 0.033) on extended femur scans. No other p value was found to indicate significace between exended femur scans displaying peaks greater than one millimetre and smoking, glucocorticoid use, alcohol intake ≥14 units per week, HRT, PPI, SSRI, thyroxine or AA/AI use.

Table 4.3 Patient demographics of individuals scanned between September 2018 and March 2019, split by peaks <1mm and >1mm as identified by GE Lunar extended femur DXA scan software.

| | | Peaks – No | | | | Peaks - Yes | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Male | | Female | | Male | | Female | |
| | | Mean | Count | Mean | Count | Mean | Count | Mean | Count |
| BMI (mean) | | 28.0 | | 26.9 | | 28.2 | | 28.3 | |
| BP | | | 68 | | 469 | | 11 | | 102 |
| HRT | | | 6 | | 421 | | 1 | | 108 |
| Alc | | | 70 | | 67 | | 28 | | 13 |
| Smoking | Past | | 163 | | 520 | | 50 | | 128 |
| | Present | | 52 | | 154 | | 16 | | 52 |
| PPI | | | 140 | | 522 | | 37 | | 127 |
| Thyroxine | | | 15 | | 233 | | 4 | | 64 |
| SSRI | | | 18 | | 181 | | 10 | | 52 |
| GC | | | 133 | | 376 | | 40 | | 109 |
| AA/AI | | | 5 | | 114 | | 1 | | 21 |
| Age (mean) | | 65.1 | | 66.8 | | 65.8 | | 66.7 | |

BMI - body mass index kg/m², BP – Bisphosphonate use, HRT – Hormone replacement therapy past or present, Alc – alcohol ≥14 units per week, PPI – proton pump inhibitor, SSRI, selective serotonin uptake inhibitor, GC – glucocorticoids, AA/AI – anti androgen/aromatase inhibitor.

## 4.2 Positive and negative predictive values of AFF

There have been five cases where it was felt there was sufficient clinical doubt on extended femur DXA imaging of peaks seen (true positives) while scanning in the space 12 months, and 928 false positives identified by the scan software on extended femur scanning, which were subsequently downgraded to normal on visual assessment by the scan operator and Rheumatologist, from a total population of 5176 patients. The 5176 patients are calculated by extrapolating the numbers from the 6 month initial data collection and multiplying by two to provide data for a 12 month period. All scans are visually assessed for peaks and irregularities at the time of reporting, allowing identification and referral for further tests where necessary The false positives are based on visual inspection of automated scan software measurements > 1 mm. No patient had follow-up femoral imaging as a result of software cortical measurement alone, because the visual assessment of the peaks by the operators and reading clinicians did not provide sufficient clinical suspicion based on the image to warrant further imaging. This leaves 4243 patients as true negatives, although it has yet to be ascertained if any false negatives exist, and would only come to light if a patient had a DXA scan prior to suffering from an AFF, however there is acceptance that a test with high specificity is less likely to produce false negative results [237].

| | | Peak | No peak |
|---|---|---|---|
| Number<br><br>5176 | Peaks ≥ 1mm<br><br>n. 933 | True positive<br><br>n. 5 | False positive<br><br>n. 928 |
| | Peaks <1mm<br><br>n. 4243 | False negative<br><br>n. 0 | True negative<br><br>n. 4243 |

Table 4.4. Breakdown of DXA scans with peaks ≥ 1mm and peaks <1mm – representing false positive and true negative findings, extrapolated to one year from six months scan data.

Based on one year's data, using the figures presented in table 4.4, a calculation was made of the positive and negative predictive value of extended femur DXA scan results. All scans acquired over the six month period were visually assessed by the operator and the reporting clinician. Alongside this, sensitivity and specificity calculations were also made, as shown in table 4.5, demonstrating the high sensitivity and negative predictive value of extended femur scanning, giving confidence that the patient does not have any indication of iAFF on the imaging acquired. Specificity values indicate the scan software produced a high number of false positivies with a large number of patients

exhibiting peaks greater than 1mm, which were found to relate to anomalous identification of the femoral cortex by the scan software.

Table 4.5 Sensitivity, specificity and predictive value of extended femur scanning and prevaence of software detected peaks , calculations extrapolated to one year from six months scan data.

| | Value | 95% CI range |
|---|---|---|
| Sensitivity | 100% | 47.82% – 100% |
| Specificity | 82.1% | 80.98% - 83.09% |
| Positive predictive value (PPV) | 0.01% | 0.051% - 0.057% |
| Negative predictive value (NPV) | 100% | |
| Accuracy | 82.1% | 81.0% - 83.11% |
| Prevalence of iAFF | 0.1% | 0.03% - 0.23% |

CI – Confidence Interval, iAFF – incomplete atypical femoral fracture

Over a period of six months, no peaks considered as suspicious were identified in any extended femur scan. Over the subsequent six month period five patients had extended femur scans performed where a suspicious peak was identified and investigated. These figures represent the very low prevalence of incomplete atypical femoral fracture found using extended femur DXA scans over the course of six months, which led to the data being extrapolated to one year. This allowed the inclusion of the suspicious peaks in the presented data.

## 4.3 Individual cases.

There follows a summary of all five cases of peaks found in DXA scans during 2019 which were thought to be suspicious both using scan software peak images, peak measurements greater than 1mm and also on visual analysis by operator/reporting Rheumatologist. These five patients were investigated initially using radiographs to further assess the femoral cortex. A summary of patient characteristics is found in table 4.6.

Table 4.6 Patient demographics overview of five patients identified with suspicious peaks ≥ 1mm on extended femur DXA scan.

| ID | Age | BMI | Height (cm) | Weight (kg) | peak position (mm) | peak size (mm) |
|---|---|---|---|---|---|---|
| 1 | 80 | 35 | 154.7 | 84 | 220 | 3.6 |
| 2 | 72 | 30.2 | 164.7 | 82 | 200 | 3.1 |
| 3 | 79 | 30.7 | 162.5 | 81 | 110 | 2.0 |
| 4 | 72 | 28.2 | 161.1 | 73.1 | 180 | 3.3 |
| 5 | 77 | 29.4 | 162.8 | 78 | 205 | 1.5 |

Cm – centimetres, mm – millimetres, kg – kilograms, BMI – body mass index, ($kg/m^2$).

### 4.3.1 Case one.

Patient number one was scanned in March 2019, a Caucasian female, aged 80 years, with a BMI of 35. Alendronate was commenced in 2011, following a DXA

scan diagnosing osteoporosis, with good self-reported compliance. Past medical history included lumbar spine fractures, short courses of oral glucocorticoids, and hypothyroid treated with levothyroxine since the 1990's. The follow up scan was requested as the patient had suffered further fractures of lumbar spine on x-ray.

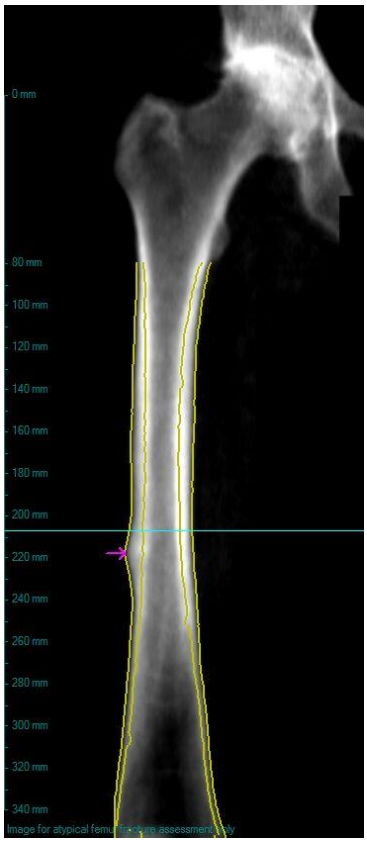



Figure 4.2. Case one, displaying a suspicious peak on extended femur DXA scan at 220 mm, highlighted by arrow.

During the extended femur scan, a peak was observed on the cortex of the right femoral shaft at 220 mm, as shown in figure 4.2. A suggestion was made in the scan report that the patient be referred for bilateral femoral x-rays to rule out the possibility of iAFF. This was done in the same month, with the reporting radiologist mentioning an "organised periosteal reaction on the lateral side of the middle third of the femoral shaft, aetiology unclear". A referral was made to orthopaedic department on this basis. The patient is awaiting follow up with an

orthopaedic surgeon, but this has been delayed by the temporary suspension of non-urgent appointments due to COVID-19.

### 4.3.2 Case two.

Case number two was female, Caucasian, aged 72 years with a BMI of 30.2. No prodromal symptoms were reported, and the patient considered herself very active, participating in regular weight bearing sports and high impact exercise activities. Alendronate had been prescribed for 10 years to 2012, with excellent compliance, and recommencement of Alendronate in 2014. Calcium and Vitamin D had been prescribed from 2002. The past medical history given: HRT for five years, previous smoker having given up around the age of 30, hip fracture in 2005. Only the right femur was scanned on account of this. When the extended femur scan was taken, there was a clear peak of 3.1 mm in the midshaft of femur at around 200 mm from tip of greater trochanter, as shown in figure 4.3.

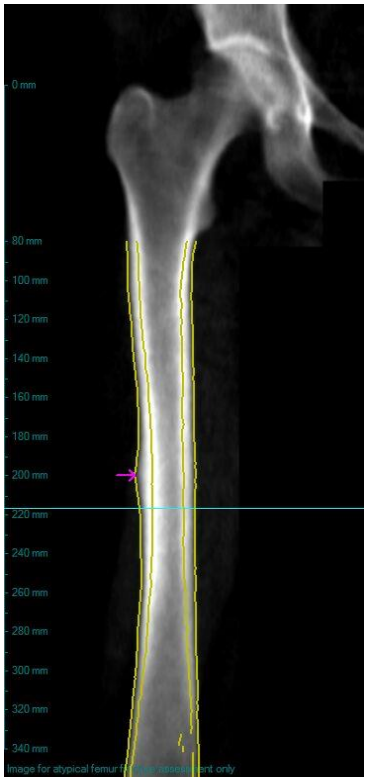



Figure 4.3 Case two displaying a suspicious peak at 200 mm on extended femur DXA scan, highlighted by arrow.

As this patient was attending the one-stop metabolic bone clinic, she was seen by a consultant rheumatologist and sent for x-ray of bilateral femora at an outpatient clinic the same day. This identified bilateral peaks at similar levels. An urgent referral was sent to orthopaedics. The patient has been followed up at three monthly intervals, with MRI imaging to assess any changes to the beaking sites, and conservative management agreed between surgeons and the patient. Follow up is now on hold due to suspension of clinical activity due to Covid-19 pandemic.

### 4.3.3 Case three.

Case number three, a Caucasian female, aged 79 years with a BMI of 30.7 and a never smoker. Osteoporosis was diagnosed in 2007, with calcium and Vitamin D had been prescribed from 2009, Alendronate had been prescribed on two separate occasions, but the patient found these difficult to tolerate.

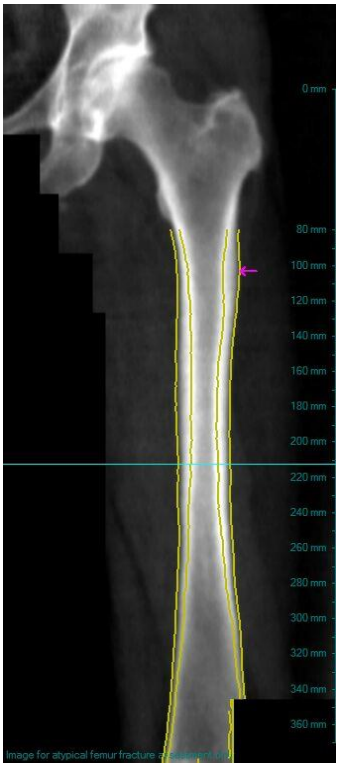



Figure 4.4 Case three displaying a peak at around 100 mm on extended femur DXA scan, highlighted by arrow.

Denosumab six-monthly injections were prescribed in 2014, tolerance and compliance were excellent. Previous medical history: menopause age was self reported at 42-43 years, with no HRT, oral glucocorticoids for around seven years, as treatment for asthma and also polymyalgia rheumatica, previous vertebral fractures at T11 and T12 on radiographic imaging.

On extended femur scanning, a peak of 2 mm was identified at around 100 mm from tip of greater trochanter, as shown in figure 4.4, an area which was covered in two previous scans also. The peak was observed at 0.5mm in 2007, increasing to 1.3 mm in 2012. As a consequence of the increasing peak size, the patient was referred for bilateral femoral x-rays. The subsequent imaging

report did not identify any features consistent with iAFF, with no follow up recommended. The area of the distal lateral femoral shaft which appears to be stepped is due to a software facility used to maximise image quality, and has no effect on the cortical measurement above this.

### 4.3.4 Case four.

Case number four was female, Caucasian, aged 72 years with a BMI of 28.2. Previous medical history included a six month period of HRT, oral glucocorticoids from 1995 to treat sarcoidosis, warfarin from 2005 following a deep vein thrombosis, and home oxygen for several years to 2019. Age at menopause was 50. A number of different bisphosphonate drugs were prescribed from 1995, along with calcium and Vitamin D, however the patient did not find bisphosphonates to be agreeable, and took irregularly. In 2014, a subtrochanteric fracture of the left femur was surgically fixed, therefore only the right femur was scanned.

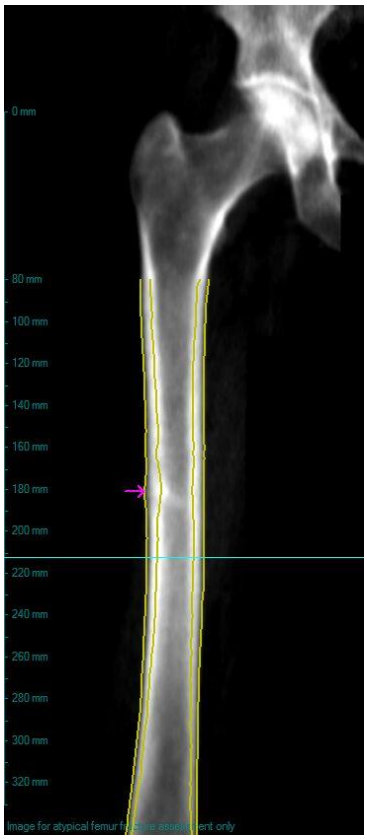



Figure 4.5 Case four extended femur DXA scan showing peak at 180 mm, highlighted by arrow.

On DXA scanning, a peak of 3.3 mm was identified on the lateral femoral cortex at 180 mm from the tip of the greater trochanter, as shown in figure 4.5. This was especially concerning, given that the lady had been prescribed long term glucocorticoid therapy, warfarin, limited mobility due to oxygen requirement and having suffered a previous subtrochanteric fracture five years previously.

A referral was made on this basis for bilateral femoral x-rays following the reporting of the DXA scan; however the patient became acutely unwell and died before any further investigation was undertaken.

### 4.3.5 Case five.

Case number five was female, Caucasian, aged 77 years with a BMI of 29.4, menopause age was self reported as 47 years. Calcium and Vitamin D supplementation was commenced in 1998, and continued at a rate of 1 tablet per day, Alendronate was prescribed from 1998 to 2004, then restarted in 2012. No report was made of prodromal groin or thigh pain; however a right hip replacement was undertaken for osteoarthritis several years earlier. Past medical history: past smoker, family history of hip fracture in sister, who was also diagnosed with osteoporosis, breast cancer diagnosed 2002, cervical cancer 2016, followed by bowel cancer in 2019, with known metastatic spread to liver. On DXA scanning, a peak was seen on the lateral cortex of the left femur at around 200 mm from tip of greater trochanter, measuring 1.5 mm, as shown in figure 4.6. This was viewed as suspicious, in the context of bisphosphonate treatment, and the patient was referred for bilateral femoral x-rays.

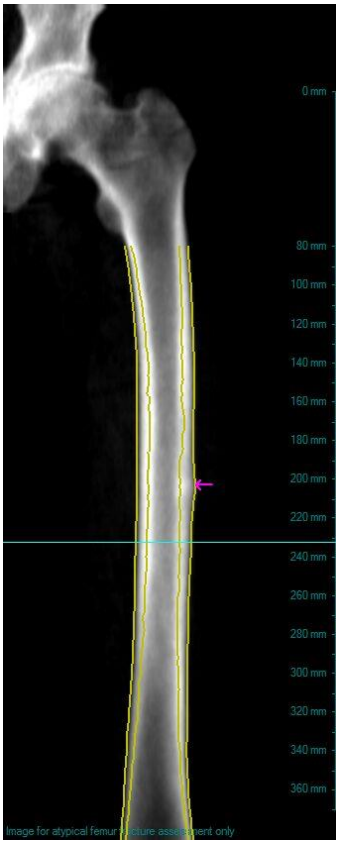



Figure 4.6 Case five with suspicious peak at 205 mm on extended femur DXA scan, highlighted by arrow.

The x-rays and subsequent imaging report highlighted a peak at a similar point of the femoral shaft, but with a differential diagnosis of metastatic deposit, suggesting nuclear medicine imaging to confirm this.

A radionuclide scan was performed which confirmed the presence of widespread metastatic disease, including the area of femoral midshaft identified as concerning on conventional imaging. The patient declined further medical intervention.

### 4.4 Ten year incidence data of AFF from hip fracture data 2008 – 2018.

Statistics from NHS Grampian health intelligence data were reviewed covering the period between 2008 and 2018, for patients aged 50 years and over with an ICD 10 coding for femoral fracture. This yielded a total of 7102 patients over the 10 year period. From this, in accordance with the revised ASBMR definition of AFF [199], those with fractures of neck of femur (n. 483), pertrochanteric (n. 1052) and multiple femoral fractures (n. 3) were excluded. Itemised in figure 4.8 are the numbers of patients whose imaging required further investigation, totalling 564. This yielded a potential AFF rate of 2% when these fracture sites are discounted.

Typically, AFFs are found in the subtrochanteric or femoral shaft region and should be coded as such using ICD 10 codes S722 and S723 for ease of identification. It is possible some AFFs may be incorrectly coded as neck of femur, and therefore not identified by this study. There were also several imaging sequences which were coded as shaft of femur, but when the radiographs and radiology reports were examined these were actually humeral

fractures. One barrier identified to the extraction of AFF numbers from femur fracture data was the lack of an ICD code specifically for AFF. Incorrectly coded fractures could lead to AFFs not being identified from health intelligence data.

On assessment of clinical information and viewing radiographs, 13 patients were identified as suffering from AFF. Eight patients were coded as having subtrochanteric fractures, four were coded as femoral shaft fracture and one coded as “fracture of femur, part unspecified”. This was found to be within the subtrochanteric region on examination of radiographs. The rate of AFF in NHS Grampian over the ten year period 2008 to 2018 was calculated as 0.18% (n. 13) of the total number of patients aged 50 years and over and identified as having a femoral fracture (n. 7102). A breakdown of fracture numbers per area over the ten year period is shown in figure 4.8. The approximate annual incidence of femoral fracture within NHS Grampian is 0.15% of the population, or 710 fractures, with over 90% of these found at the femoral neck or pertrochanteric region. All patients reviewed were over the age of 50 years, and with assessment of images flagged as femoral shaft fracture, in keeping with ASBMR criteria [199], which may have discounted patients with a fracture labelled as insufficiency, which appears to be how atypical femoral fractures have been reported historically in this health board if there is no record of bisphosphonate exposure. These may exhibit elements of AFF but not considered for visual assessment as part of the data collection process, which potentially skewed the data presented.

All patients affected were Caucasian, with a mean age of 74.9 years, 92% female, with only 15% of patients complaining of prodromal pain ranging from a few days to several months in duration. Over half the patients affected had

been prescribed glucocorticoids, for various medical conditions. All patients had been exposed to bisphosphonate therapy, although it was difficult to ascertain exact durations, from the information available the timescales vary from 2 – 13 years, with a median of nine years. All fractures were repaired using intramedullary nailing, with 38.5% of patients suffering complications of non-union, fracturing of the nail or both. Patient demographics are listed in table 4.6 . One patient suffered a complete contralateral AFF at a similar level to the index fracture, a full thickness fracture which required intramedullary nailing around six months following the initial fracture. On review, this was identifiable on the MRI imaging performed prior to surgical repair of the index fracture. The area of abnormality is highlighted in figure 4.7 in red. During the period between the index and contralateral fractures, the patient continued on bisphosphonate medication.

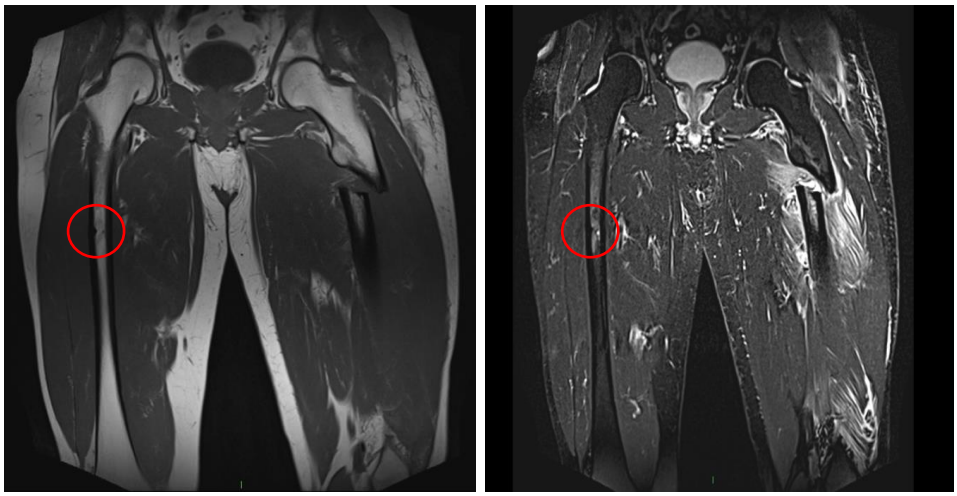


Figure 4.7 Magnetic resonance Imaging identifying contralateral iAFF of the right femur following index fracture of the left femoral shaft.

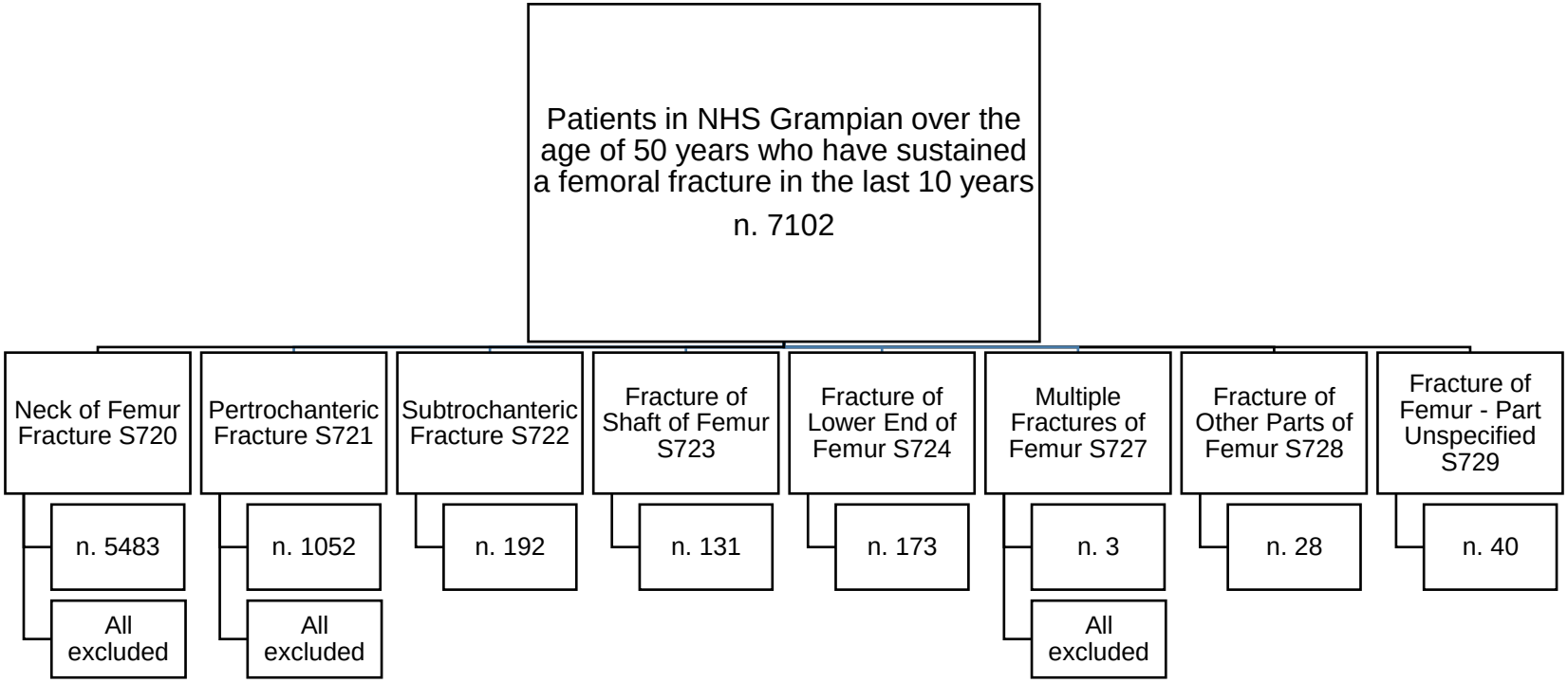



Figure 4.8 Femoral fracture incidence in NHS Grampian between 2008 and 2018, separated to fracture regions.

Table 4.7 Available patient history of those identified with AFF within NHS Grampian 2008 to 2018.

| Age | Gender | Region | MOI | Prodromal Symptoms | Right/Left | Steroid Use & Duration | Bisphos Use & Duration | Management | Complications |
|---|---|---|---|---|---|---|---|---|---|
| 71 | Female | Subtrochanteric | Leg gave way | No | Right | N/A | Yes – approx. 8 years | IM | Non-union, IM nail fracture |
| 70 | Female | Subtrochanteric | Fall | No | Right | N/A | Yes – approx. 8 years | IM | Non-union, IM nail fracture |
| 72 | Female | Subtrochanteric | Fall | Yes – left thigh pain for several months | Left | Yes – insufficient information | Yes – approx. 11 years | IM | |
| 64 | Female | Subtrochanteric | Leg gave way | No | Left | Yes – approx. 20 years | Yes – approx. 11 years | IM | Non-union, IM nail fracture |
| 55 | Male | Subtrochanteric | Fall | No | Left | Yes – approx. 25 years | Yes – approx. 13 years | IM | |
| 80 | Female | Subtrochanteric | Slipped, fell downstairs | No | Right | N/A | Yes – approx. 9 years | IM | Non-union, IM nail fracture |
| 88 | Female | Subtrochanteric | Lost balance | No | Right | Yes – approx. 11 years | Yes – approx. 11 years | IM | Non-union |
| 75 | Female | Subtrochanteric | Fall | No | Left | Yes – 3 short courses in 1 year | Yes – insufficient information | IM | |
| 79 | Female | Shaft of Femur | Fall | No | Right | Yes – insufficient information | Yes – insufficient information | IM | |
| 84 | Female | Shaft of Femur | Fall | No | Left | Yes – insufficient information | Yes – approx. 3 years | IM | |
| 80 | Female | Shaft of Femur | Lost balance | No | Right | N/A | Yes – approx. 2 years | IM | |
| 81 | Female | Shaft of Femur | Lost balance | No | Left | N/A | Yes – approx. 9 years | IM | |
| 75 | Female | Fracture of Femur – Part Unspecified | Fall transferring from chair | Yes – right thigh pain 2 days | Right | N/A | Yes – approx. 2 years | IM | |

MOI – mechanism of injury, bisphos – bisphosphonate, IM – Intramedullary nail fixation of fracture, N/A – not applicable, Approx – approximately.

## 4.5 Summary.

The section has focussed on the service evaluation and patient demographic of the service within NHS Grampian, presenting results of the population studies which have been undertaken in relation to the extended femur scanning software and its routine clinical use in the department. The recent history of AFF within NHS Grampian gives a perspective on the scale of the rare but serious complication of AFF alongside the implications and complications of fracture repair in the patient cohort affected, and the likely association of bisphosphonate use and prolonged glucocorticoid use in this patient group. The next section will present the results of the use of the extended femur scanning software in clinical practice.

# 5 Results – Departmental audits and in-vivo precision study.

This section will provide an overview of the results gathered from the precision study, and related audits as detailed previously in methods section 2. This forms part of the evaluation and assessment process of the GE Lunar extended femur DXA scan software.

## 5.1 Femur scan positioning and technical analysis audit.

30 scans selected at random from 5 operators across 4 scanners used within the department, as outlined in methods section 2.3. Scans were analysed on criteria supplied by GE, which sets out expected standards for assessing proximal femur scanning, and for assessment of extended femur scans.

The summarised results of the positioning and technical analysis audit are presented in table 5.1.

Table 5.1 Results of audit on femur scan positioning and technical analysis of 30 extended femur DXA scans.

| Assessment criteria | Number correctly identified/scanned (%) | |
|---|---|---|
| Elimination of patella and supracondylar flare | 23 | (77) |
| Mid femoral line bisecting the femoral head | 30 | (100) |
| Sufficient shaft of femur evident | 30 | (100) |
| Acetabulum included fully in scan field | 25 | (83) |
| Lesser trochanter minimised | 30 | (100) |
| Elimination of ischium and greater trochanter from measurement area | 28 | (93) |
| Bone mapping accurate | 29 | (97) |
| Neck of femur box correctly placed, at 90° to femoral neck, all corners in soft tissue | 28 | (93) |
| Is the femur vertical in the field of view | 23 | (77) |

Results are presented as frequency (%)

The scan audit revealed that in most cases, scans were acquired and analysed according to departmental protocol, training and good clinical practice.

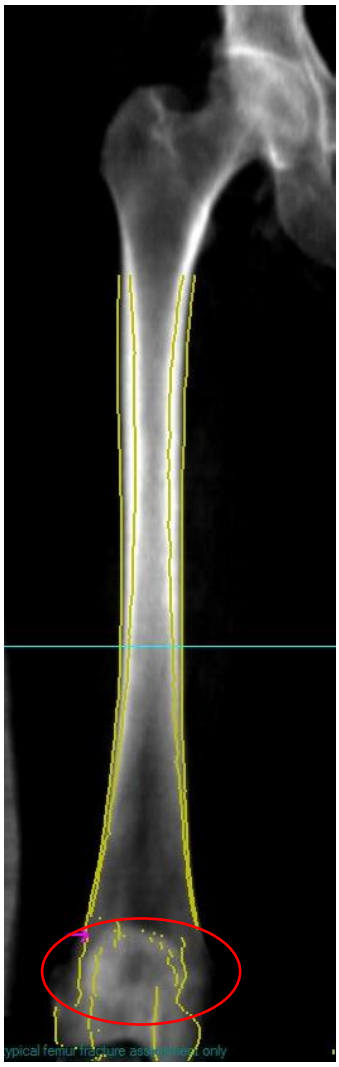


Figure 5.1 Inclusion of patella in extended femur scan field, incorrectly identified as a peak on DXA scan.

In several areas the audit identified good practice in 100% of scans: placing of the mid femoral line to bisect the femoral head, sufficient shaft of femur evident and lesser trochanter is minimised. Over 90% of scans also demonstrated excellent bone mapping, with iscium and greater trochanter eliminated from the neck of femur measurement area, and the neck of femur box placed at 90° to the neck of femur line. Several areas fell below the levels of 90% expected: placing the femur vertical in the field of view, elimination of patella and distal metaphysis of femur from the scan field, and the lack of full acteabulum from the scan area. The positioning of the femur can be dependent on the patient

habitus and ability to abduct and rotate hips, and therefore can be difficult to achieve in every situation.

However, the positioning of the proximal femur and assessment of the lateral cortical border is reliant on best possible positioning to allow reproducibilty of measurements and subsequent results. One operator appeared to misinterpret the training and scan start point, and purposely started scanning at a point more distal to the patella in order to include it in the scan image, as demonstrated in figure 5.1. This has the consequence of the scan software attempting to measure the cortex of the patella, giving false positive peaks.
In areas of less than 90% compliance, it was felt that patient habitus may have played a minor role in positioning of the femur, however the scan checklist used for audit of scan positioning and technical analysis found in appendix 9.10 has been shared among operators to ensure they can assess the quality of their scans as they are acquired, thus enabling repeat where necessary. This checklist also includes the inclusion of acetabulum to the pelvic brim, and explanation that this facilitates the measurement of hip-axis length which is useful in some research settings.

In-house individual training has already been undertaken to reinforce that operators should not include patella in the scan field, and use it only as a centring point for scan commencement. The informal one to one training included the discussion of the difficulties that inclusion of patella creates for the extended femur scan software and the creation of artificial peak measurements. Further audit of this will be required to assess the efficacy of these measures, and instigate further staff development of scanning technique where necessary.

## 5.2 Visual assessment of extended femur scans for beaking.

Four individuals experienced in viewing DXA scans independently visually assessed the lateral cortex of the femur from just below the level of the lesser trochanter to distal end of the shaft of femur on previously reported individual scans from the file provided. An opinion was then recorded on whether any signs of suspicious lateral cortical thickening/beaking were visible, and record as yes/no on a spreadsheet. This was based on the image alone, without viewing the beaking measurement tab of the scan software, no patient history, or consulting with colleagues, avoiding external influence. The participant characteristics are similar to those of the precision study and also the population study in section 3.1.

The results of visual assessments of 30 individual femur scans were collated as described in methods section 2.4, and compared with the results of the automated scan software measurement. A summary of patient characteristics is displayed in table 5.2. It was established from the data collected that there was no ground truth, as there was no agreement between viewers. Abnormalities of the lateral cortex of the femur are indicated as focal thickening at either the endosteal or periosteal edge of the lateral femoral cortex and peaks which are located between the lesser trochanter and the supracondylar flare at the distal femur [16]. These are the key areas measurable using densitometry, and do not rely on a fracture line being visible. Should a focal thickening be identified on the lateral femoral cortex, additional imaging is recommended. Based on scan software cortical measurements, 33% of scans viewed exhibited peaks on the endosteal edge of the cortex, with peak

measurements greater than 1mm, none of which were deemed to have any suspicious features.

| | | | |
|---|---|---|---|
| Test result<br><br>n. 30 | Perceived abnormality on scan viewer (software) | True positive<br><br>n. 0<br><br>(0) | False positive<br><br>n. 10<br><br>(10) |
| | No perceived abnormality on scan viewer (software) | False negative<br><br>n. 0<br><br>(0) | True negative<br><br>n. 20<br><br>(20) |

Table 5.2. Breakdown of DXA scan assessment of femoral cortex by four viewers, compared with automated scan software measurements.

These results yielded a specificity result of 66.7%, with a confidence interval between 47.2% and 82.7%, and a negative predictive value of 100%. No further imaging was undertaken in any of these cases, as visual assessment had been carried out at the time of reporting and all peaks > 1 mm identified as having been erroneously created by the scan software.

Had further investigation been required, plain bilateral femoral radiographs are first line investigation, being cost effective and with good general availability. The largest peak size measured 3.7 mm, which was considered abnormal by one viewer. This was identified as a software anomaly, not representative of a true change in cortical thickness.

Table 5.3 Participant characteristics of peaks as assessed by four viewers.

| | Male (10) | Female (20) |
|---|---|---|
| Median age yrs. (range) | 68 (38 - 79) | 71 (30 - 95) |
| Median height cm (range) | 171.15 (162.5 – 183.5) | 159.5 (151.3 – 168.2) |
| Median weight kg (range) | 86 (68 - 108) | 60.25 (40.5 – 113.5) |
| Median BMI kg/m$^2$ (range) | 28.9 (24.1 – 35.3) | 24.25 (17.5 – 42.2) |
| Median Beaking Index mm (range) | 0.55 (0.2 – 1.4) | 0.65 (0.2 – 3.7) |

Height in cm, weight in kg, BMI kg/m², beaking index millimetres.

The criterion for reviewing images assesses the scan image in conjunction with the AFF software revolves around the lateral cortex of the femur and specifically the periosteal border of the same. Viewers were making assessment of the lateral cortex of the femur; ensuring continuity of the periosteum, with no abnormal lumps or bumps. The periosteal border of the lateral cortex is highlighted in figure 5.3. If any abnormalities are identified, are they in the area of the femoral shaft or subtrochanteric area? Is there any indication of involvement of muscle insertion if the suspicious area is in the subtrochanteric region? Is there anything in the patient history which would arouse suspicion of AFF – such as bisphosphonate use, glucocorticoid use? Is there any history of previous femoral damage, even in childhood?

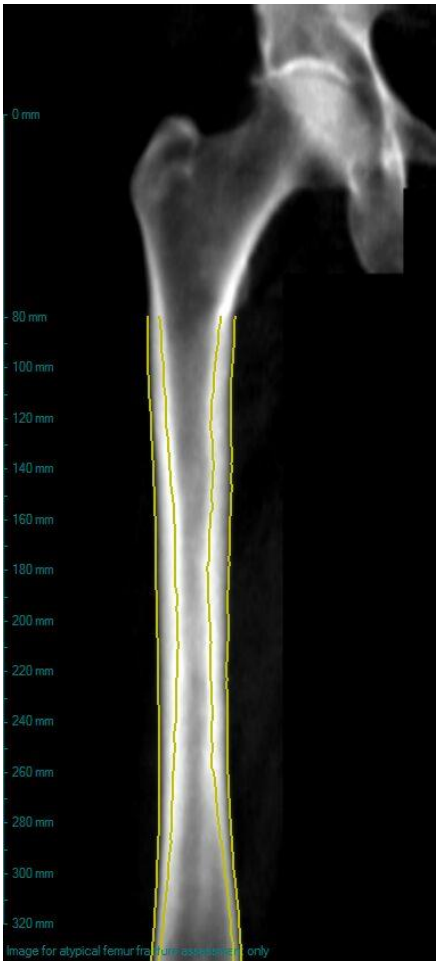



Figure 5.2 DXA scan image with the periosteal border of the lateral femoral cortex highlighted.

Viewer one recorded 0 scans from 30 as having suspicious features of beaking on the scan, with the second querying only 2 of the images as having features worthy of further review. There was less agreement between viewers three and four, where one identified eight images as having suspicious features, and the other finding three. On visual assessment, none of the images used were thought to have suspicious features at time of scanning and reporting, however several of the images were considered as exhibiting false positive peaks as measured by the scan software. Five of eight scans identified as abnormal by viewer four exhibited false positive peaks of greater than 1mm. Findings of the assessment are presented in table 5.3. Consequentially, an assessment was made of the position of the femur on each scan which was subjectively selected

as displaying beaking, as it was felt that incorrect positioning of the femur may contribute these findings.

Table 5.4 Beaking assessment of DXA scans by four viewers

| | Scans felt to be normal | Scans felt to be abnormal | % scans felt to be abnormal | % scans marked abnormal which may be positioning related |
|---|---|---|---|---|
| Viewer 1 | 30 | 0 | 0% | - |
| Viewer 2 | 28 | 2 | 7% | 50% |
| Viewer 3 | 22 | 8 | 27% | 12.5% |
| Viewer 4 | 27 | 3 | 10% | 33% |

Percentage agreement was calculated at 89%, across all viewers. Viewers one and two had 93% agreement across cases, where viewers three and four had a lower agreement at 63%. Cohen's Kappa scores for both groups were below zero, viewers one and two were -0.034, three and four -0.224. The 95% confidence interval range was found to be -0.023 – -0.046 for viewers one and two, and -0.213 - -0.236 for three and four. The calculation of Cohen's kappa scores show a disparity in results, due to the method of calculation, where observed agreement and chance agreement are used to calculate a result, taking into account the potential for guessing by raters, leading to excessive lowering of agreement. However in a clinical research environment a kappa score cannot be relied upon as a basis for changes to clinical practice, potentially having a negative impact on patient care and clinical outcomes, owing to its leniency and the implication that lower scores are acceptable [238]. All kappa scores have returned results below 0, indicating no agreement better

than chance between raters [234]. However as the sample size is at the lower end of assessment recommendations, the results produced are no better than coincidental, therefore unreliable; a much larger sample size is likely to give more accurate results [234]. As the scan assessments were all carried out by experienced staff, who were asked to give a yes or no answer to one question, the use of percentage agreement provides a more accurate overview of the visual analysis of beaking on extended femur scans. This may suggest that there is a requirement for a more prescriptive checklist to be provided for scan assessment to ensure all viewers are assessing scans in the same manner.

### 5.3 Scan analysis – software automatic beaking index measurement.

A group of 30 randomly allocated single extended femur DXA scans were re-analysed in triplicate, from across all scanners and operators within the department, as detailed in methods section 2.5. Beaking index measurements were taken from automatic software scan analysis and recorded to one decimal place. Scans were automatically re-analysed using the scan software on two further separate occasions to determine the reliability of the scan software. All scans recorded identical measurements to one decimal place, exhibiting no precision error. Measurement can only be taken to one decimal place on the scan viewing screen as this is the limit of the scan software. This reassures operators that the scan software is consistent in the analyses of peaks on scan images.

## 5.4 Precision study.

An in-vivo precision study of 30 patients referred for routine DXA scanning measured the short term operator precision of extended femur scans as outlined in methods section 2.2. The study was undertaken using BMD measurements obtained at neck of femur and total hip, along with beaking index measurements on extended femur scans.

### 5.4.1 Participant characteristics.

The participant group for this study had an age range of 49-89 years, participant characteristics are displayed in table 5.4. Male participants made up 37% of the total scanned, slightly higher than the 21% of total patients scanned from the general departmental data found in section 4.1. Participants had a median age of 70 years, slightly older than the 66.4 years median age of those scanned in section 4.1 and had a median BMI of 26.8, similar to those in data collection with a BMI of 26.5. Three female participants and one male participant were found to be osteoporotic.

Table 5.5 Participant characteristics – in-vivo precision study.

| | Male (11) | Female (19) |
|---|---|---|
| Median age yrs. (range) | 70 (49-78) | 67 (49-89) |
| Median height cm (range) | 175.4 (163.6-177.6) | 157.9 (148.5-175) |
| Median weight kg (range) | 86 (71-130.9) | 68.75 (47.5-100) |
| Median BMI kg/m² (range) | 29.8 (24-42) | 26.5 (20.4-36.8) |
| Osteoporotic on scan (%) | 1 (9.1) | 3 (15.8) |
| Osteopenic on scan (%) | 3 (27.3) | 13 (68.4) |
| Normal BMD on scan (%) | 7 (63.6) | 3 (15.8) |
| Patients with mean Beaking index >1mm (%) | 4 (36.4) | 2 (10.5) |

### 5.4.2 Precision calculations.

The results at both sites indicate precision to be well within the parameters set by the ISCD. Accepted figures quoted by the ISCD for 95% least significant change (LSC) for femoral neck is 6.9%, and total hip 5.0% [236], as displayed in table 5.5, the actual figures for femoral neck precision of 5.68% and 3.96% for total hip measurement, again displayed in table 5.5 . Least significant change is calculated by multiplying the RMS CV by 2.77, giving a 95% confidence interval, and represents the required change in measurements to indicate a true biological change in a patient, which cannot be attributed to measurement error. The mean and difference of beaking index measurement error were calculated

using the Bland-Altman method of 95% limit of agreement [239] and plotted as shown in figure 5.3.

Table 5.6 In-Vivo precision study results at total hip and neck of femur BMD and beaking index values.

| | Total hip BMD | Neck of femur BMD | Beaking Index (mm) |
|---|---|---|---|
| RMS SD | 0.011 | 0.015 | 0.473 |
| RMS CV | 1.43 | 2.05 | 38.18 |
| LSC % | 3.96 | 5.68 | |

RMS - Root mean squared, SD – Standard deviation, CV – coefficient of variation, BMD – bone mineral density, mm – millimetres.

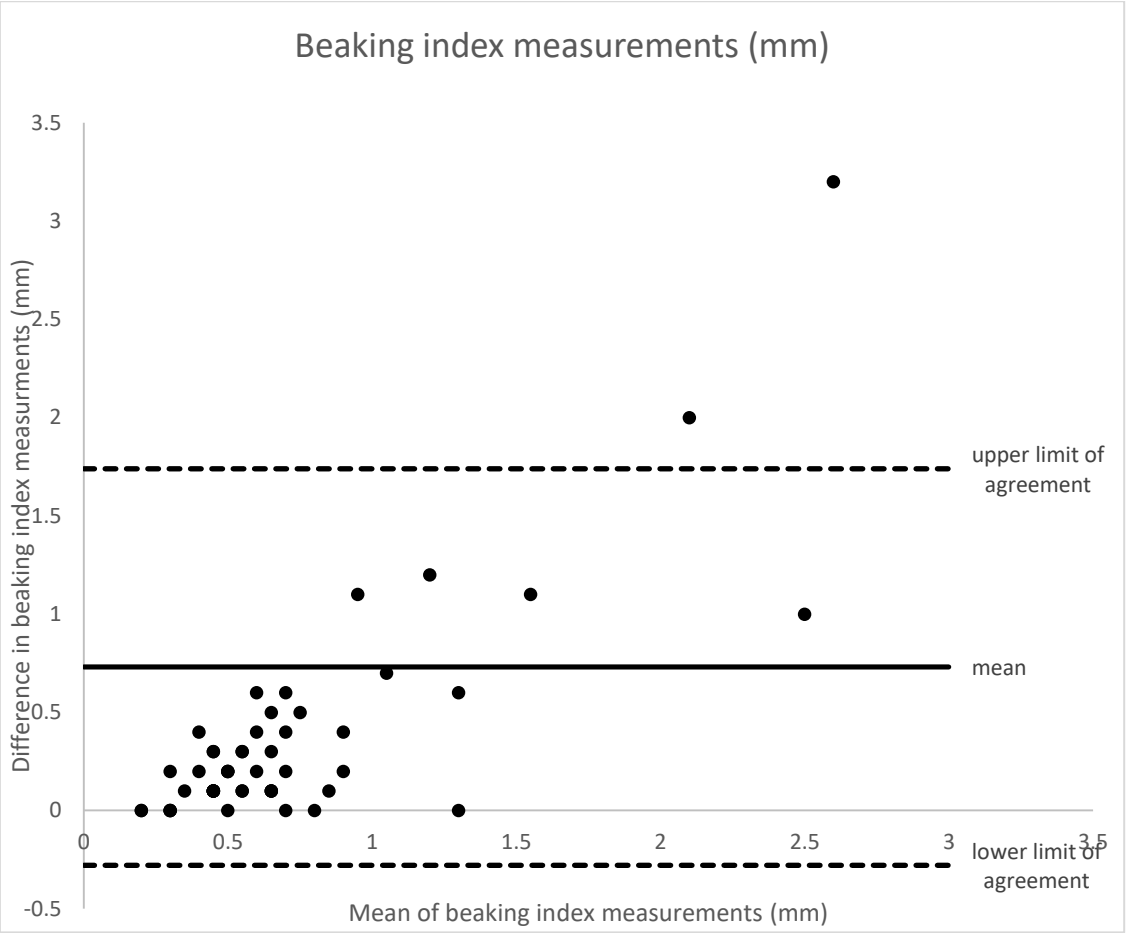



Figure 5.3 Bland-Altman plot displaying the precision study beaking index, measurements in millimetres.

As demonstrated by the Bland-Altman plot in figure 5.3, 28 of 30 duplicate beaking index measurements fell within two standard deviations (SD) of the mean, or 93.3%. This is only marginally lower than the expected 95% of points falling within two SD of the mean [240]. Six participants exhibited a mean beaking index measurement greater than 1mm, and six 30 participants had a beaking index measurement difference greater than 0.5mm, quoted by GE as the error margin of measurements. The error margin of the beaking index measurement using bench phantoms was set at 0.5mm by GE, with a caveat that measurement error may be higher in a clinical population [229]. This in-

vivo precision study found the mean of the measurements on human participants to be 0.5mm.

### 5.4.3 Outliers in beaking index measurement.

One set of beaking index scan results for a female participant demonstrated a software inaccuracy in identifying the cortex of the femur, displaying a result of 4.2 mm in one scan, and 1mm in the subsequent scan. This measurement of beaking index difference was found to be out with two standard deviations, attributed to erroneous placing of cortical borders by scan software, perhaps confounded by a slight change in patient positioning as shown in figure 5.4.

Figure 5.4 DXA scan image showing duplicate scan with differing software assessment of femoral cortices.

The second outlier was similarly placed, with the scan software identifying a thickening at the endosteal border of the lateral femoral cortex on one scan, as seen in figure 5.5. Six patients scanned were found to have mean beaking

index measurements greater than 1mm; however no features suggestive of peaks or cortical thickening were identified on any scan image.

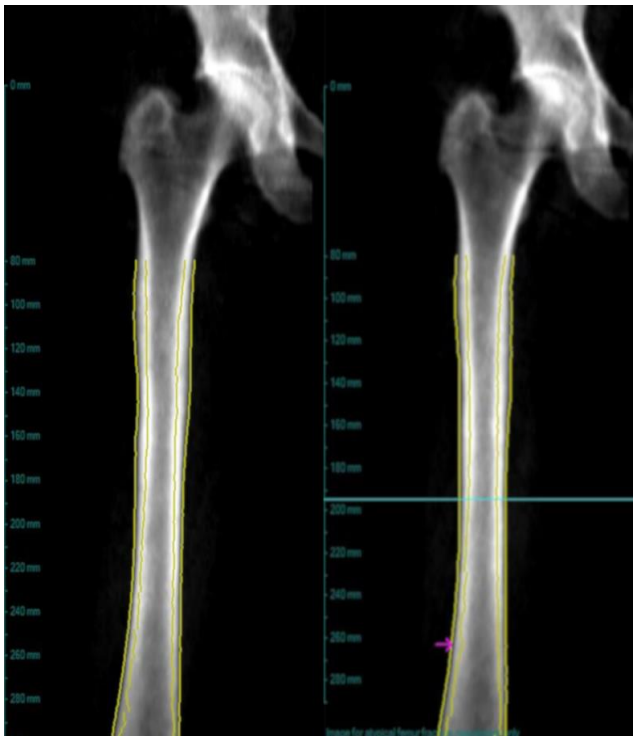


Figure 5.5 DXA scan image showing second outlier image with thickening on endosteal border of the femoral cortex.

One of these images is shown in figure 5.5, demonstrating an irregularity in the positioning of the femoral cortical margin, where the endosteal border of the lateral femoral cortex is incorrectly identified by the scan software. This created a step which the software analyses as a cortical thickening or peak.

In some cases, there was substantial measurement variation between pairs of beaking index scans, no reason was found for this aside from erroneous placement by the automated scan software, as both scans appeared similar. An example of an automated software measurement creating false positive is demonstrated in figure 5.6.

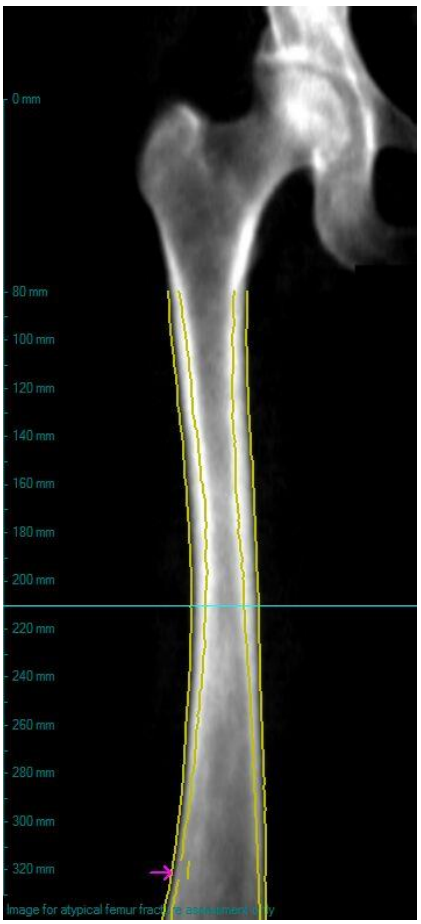



Figure 5.6 Inaccurate software identification of femoral cortex on DXA scan image.

## 5.5 Summary.

This section has presented the results of the precision study and associated audits undertaken in the assessment of the extended femur scan software when used routinely in a clinical environment. A discussion of the findings of both section three and four in the context of the available research and literature will be presented in the next section.

# 6 Discussion.

This body of work sought to investigate the incidence of AFF, underlying associations and the GE Lunar DXA extended femur scan software in clinical practice in NHS Grampian. The discussion will compare the findings of these areas in the context of available literature and published research.

## 6.1 Review of study aims.

The motivation for this study was the evaluation and assessment, in routine clinical practice, of the extended femur scanning software developed by GE. This software is designed to be used as part of routine DXA scanning to identify changes in the femoral cortex in a clinical population.

## 6.2 Demographics.

The data collected within NHS Grampian found that the demographics of patients affected by AFF was broadly comparable to similar studies undertaken in terms of age, gender, lifestyle choices and risk factors.

The age range of the group of patients identified in this body of work is in keeping with the findings of a 2013 retrospective study of radiographic imaging conducted using a Caucasian population in Sweden of a median age of 76

years [241], and slightly higher than that of a Korean-based study of post menopausal Asian women which found a mean age of 68.1 years [73].

The available research indicates that AFF affect both sexes and although the incidence of both bisphosphonate use and AFF is lower in men, they should be included in any prospective or retrospective research. The lower rates of males affected by AFF may be as a result of historically lower rates of DXA scanning in males, and association of osteoporosis as a women's disease. In a seminal study of bisphosphonate – related fractures [1], one of the nine patients included in the data set was male, who suffered from bilateral femoral shaft fractures having taken Alendronate for eight years previously, where BMD measurement had been osteopenic on commencement of therapy and remained so following cessation of treatment. A retrospective review of two years of patient data from across UK hospitals found four males affected by AFF in the study period, with half of these patients not having bisphosphonate exposure. It was noted however that of the five bisphosphonate naïve patients identified within the AFF cohort, one had glucocorticoid exposure and another had been taking methotrexate for psoriatic arthritis [242], no breakdown was available on patient gender.

Patients identified as suffering from AFF from collected data over 10 years within NHS Grampian were all found to have bisphosphonate exposure of varying lengths, which is not in keeping with data presented in the literature. Several other studies have identified patients with AFF who are bisphosphonate naïve, indicating that bisphosphonate use is not the sole mechanism for such fractures occurring [33, 212, 242]. In contrast, one study found the rate of AFF in patients not exposed to bisphosphonate was a rate of one per 150,000 patients, therefore it is possible that in comparison to this that the number of

patients studied in this case was too low (7500) to identify non-bisphosphonate related AFFs [243]. This may be as a consequence of the inexperience of the viewers, the search criteria used, the images sent for adjudication to orthopaedics remaining unclassified, or a mix of all these reasons.

The population identified as having iAFF on extended femur DXA scan in this study had a BMI significantly higher than the general scan population. Obesity has been indicated as one of multiple risk factors for AFF in other studies, regardless of ethnicity, alongside bisphosphonate and glucocorticoid exposure [73, 244, 245]. This finding was supported by a retrospective study undertaken with an Asian population found that while patients with AFF had a mean BMI of 25.1 kg/m² and not considered obese, they had a higher BMI than the study control group, who had a mean BMI of 23.5 kg/m² [246], suggesting that a BMI which is higher than the routine scan population is a significant risk factor. Evidence has been presented that a BMI >30 kg/m² can also have a confounding effect on DXA scan results, artificially altering BMD results at the hip area by +/- 2%, without certainty of whether this will elevate or reduce BMD [247]. There is a risk that this may lead to over (or under) treatment, where patients have a borderline hip BMD.

Presented within the published literature is evidence which suggests patients of Asian ethnicity are more likely to suffer iAFF and AFF at an earlier age than their Caucasian contemporaries. This theory is supported by a 2016 study undertaken in California of female patients taking bisphosphonate, also suffering an AFF, which found that Caucasian women were four years older than Asian women when diagnosed with AFF [32]. This statistic should be

interpreted with caution however, as it was indicated in the same study that Asian women were prescribed bisphosphonates around four years earlier than Caucasian women. Ethnicity was not investigated as part of this body of work, as the geographical area is a settled Caucasian population and very few Asian patients were scanned, all of the patients found with AFF or iAFF were Caucasian.

Each study documented in the available literature investigating the incidence and identification of iAFF/AFF used slightly different methodology and technology which makes direct comparison difficult, and this presented challenges in drawing any solid conclusions [73, 245, 248]. It appears in several studies that although the patient demographic was broadly similar in each, there were fundamental differences in the way each study was conducted. The use of proximal femur DXA scanning extended to its full window will measure less than half of the shaft of femur, which would mean that a significant number of femoral shaft abnormalities could be missed [15, 249]. An earlier study using the maximum scan length of conventional proximal femur DXA scanned 257 patients aged over 50 years, with bisphosphonate use of greater than 5 years [250]. The results found that 2.7% (n.7) of this specific population exhibited signs of iAFF on DXA imaging, which is high in comparison to the data acquired in this study. This patient group was considered as high risk, having been prescribed bisphosphonate drugs for five years, which is also known to increase risk by around 0.22%, when treatment is extended out to seven years [251]. Scanning of no more than half the shaft of femur, without the benefit of scan software or program designed to aid the detection of such abnormalities will prevent visualisation of all defects within the femoral shaft [249].

Only two patients from the seven identified as exhibiting abnormality on DXA were subject to onward referral for orthopaedic intervention in the form of IM nailing, the other five appear to have had no follow up or intervention. The authors accept that there are limitations to the study, small sample size, the specific group of patients chosen and the age restriction. The software used is not specifically designed to identify all AFFs through the full length of the femur, as this is a small extension of proximal femur scanning, therefore there is potential for further cases to be missed due to the lack of full length imaging. Femoral shaft fractures account for anywhere from 47% to 63.2% of AFFs, commencing the scan just proximal to the supracondylar flare allows for greatest visualisation and therefore optimal benefit [4, 75, 98].

A study undertaken in Sweden, which has a similar mainly Caucasian population, identified that 78% of patients with AFF had fractures in the femoral shaft, as opposed to the subtrochanteric area, highlighting the importance of visualising the full length of the femoral shaft [252]. This is comparable with the findings of a subsequent study which found 82.4% of iAFFs were located within the mid shaft area of femur [245], and similar to the iAFFs found within NHS Grampian using extended femur DXA scanning, 80% of which were mid shaft. It should be noted that there are numerous definitions of where measurements should be taken to classify a fracture as subtrochanteric, therefore it may be difficult to compare studies where a measurement definition has not been provided [241]. One European study found a dichotomy of fracture location, with subtrochanteric fractures more likely to occur in those with a median age of 71 years, and femoral shaft fractures in those with a median age of 80 years

[241], very much in keeping with the ages of those patients identified in NHS Grampian between 2008 to 2018 suffering AFF.

Other studies have used very specific high-risk populations which limits generalisability in a clinical population. The findings of a 2013 study identified 2.7% of a DXA scan population as having iAFF on radiological imaging [249], however in this 16 month prospective study, the patient group selected were identified as high risk of AFF, who had been diagnosed as osteoporotic and been taking bisphosphonate treatment for at least five years. These patients were scanned using the maximum length proximal femur scan window using Hologic single energy scanners, and although the BMD results may not be directly comparable to those acquired from a GE Lunar dual energy scanner, the same principles apply to the cortical measurement and identification of iAFFs. This study also found the rate of false positive to be over 4.5%, which although higher than the true positive rate, was much lower than the 20% false positive rate found using the GE Lunar scan software alone. A subsequent study using Hologic scanners and long term bisphosphate users failed to identify any patients with iAFF on DXA scanning over a further period of 16 months, using identical study methods to 2013 study [249], scanning 173 high risk patients with a view to requiring somewhere between 27 and 59 patients to find one iAFF [15].

There have been various methods documented in the measurement and analysis of the femoral cortices, with some using radiographs and measurement software, while others performed measurement on images acquired using DXA. This has led to fundamental differences between studies, making each difficult

to replicate using the extended femur scanning software, and also making direct comparisons virtually impossible. A consistent and standardised approach to future studies involving extended femur DXA scanning would allow much closer comparisons to be made, with no detriment identified to the reproducibility of proximal hip BMD measurements by extending the scan length and therefore could be utilised as a screening tool for all patients [224].

The difference between male and female beaking index results may be as a consequence of differing physical characteristics such as greater femur size and prominence of muscle insertion points in men [253], but there is no reason why this should affect the rate of peaks between male groups. It has been suggested that cortical contouring at the level of the femoral gluteal insertion could present additional difficulty in identifying iAFF at this level, as callous identification may be masked [241]. This is compounded by the assumption that peaks seen in the subtrochanteric region of a DXA scan are muscle insertion points and therefore deemed insignificant and not investigated. This may be the case in patient number three within the case studies in section 4.1, where a peak increasing in size was measured over serial scans.

In a similar study, 173 patients who were all prescribed long term bisphosphonate therapy, almost 7% of participants had abnormal findings on extended femur scanning, a quarter of which were deemed to be prominent gluteus maximus insertion points, identified using CT imaging [15]. This study performed DXA imaging, then subsequently performed a single energy femur scan of each femur remaining in position as for proximal hip scan. This adds to the time taken for the examination, and the radiation burden for the patient. Were the two examinations to be combined it would prove more efficient for the DXA service, while exposing the patient to the minimum amount of radiation

possible to answer the diagnostic question and to assess the femoral cortex [254]. The lack of any indication of AFF should not be considered as a reason to abandon the extended femur scanning software or practice, as somewhere between 3.2 and 5 per 100,000 person-years are predicted to be at risk of AFF [103].

As identified earlier in the section, direct comparison between studies is challenging, as no study has been found that examines a general population using extended femur DXA scanning, irrespective of age, sex or bisphosphonate exposure. There is also consensus that as femoral shaft imaging is novel for most patients, no definite link can be made between bisphosphonate and peaks, as no evidence is available to confirm or deny cortical thickening or abnormality prior to therapy commencement [227].

Indeed, studies have identified atypical fractures in bisphosphonate-naïve patients [2, 4, 33, 75, 76], this is in contrast to the findings of ten year data analysis in NHS Grampian, where all patients had bisphosphonate exposure of varying duration, despite bisphosphonate use not being part of inclusion criteria at the time of the audit. One study found previously unidentified beaking in around 8% of patients at bisphosphonate initiation, of unknown duration, although all patients had recently been prescribed bisphosphonates in conjunction with glucocorticoids. This would suggest benefit in examining the entire shaft of femur prior to commencement of bisphosphonate or glucocorticoid therapy to rule out any latent beaking prior to commencement of treatment [99].

### 6.3 Performance of software in clinical practice.

The extended femur scanning software provides an opportunity to combine cortical assessment of femur through an extended DXA scan covering the femur, in addition to routine bone mineral density measurements at the hip. It has been established that this has no detrimental effect on the BMD measurements, and with the addition of less than two minutes to the examination time of a dual extended femur scan, and 37 µGy to the cumulative radiation dose, it is not a major burden of time or radiation for the patient or for service delivery. It appears to be tolerated well by patients, with only minor adjustment to positioning and patient preparation required.

The negative predictive value of scans can be used to reassure patients that there is no indication of damage to the femoral cortex caused by anti-resorptive treatments, indicated as a major reason for non-adherence, non-compliance or refusal of treatment [222]. There is real concern in the patient population of the dangers of bisphosphonate therapy, with regard to atypical femoral fractures and osteonecrosis of the jaw, with one study reporting an alarming 50% drop in bisphosphonate use over a four year period [255]. The findings of a study of bisphosphonate therapy benefits indicated a risk reduction of up to 32% after two years of therapy in patients with good compliance, in contrast to an increased risk of up to 50% in those non-compliant with prescribed bisphosphonates [222]. The same study also indicated that BMD measurement had a positive influence in compliance and persistence with bisphosphonate therapy, despite the side effects. The risk of life-changing hip fracture is much greater than the risk of either of these rare but concerning side effects, with one study finding that good compliance with taking bisphosphonate drugs decreases

the risk of intertrochanteric and femoral neck fractures after one year [200]. A similar study reported that although general fracture risk continues to decrease after 2 years of therapy, the risk of atypical femoral fractures, although still very small, is reported to increase by fifty times after compliant therapy with bisphosphonates [213]. A positive predictive value of 0.01% may seem low, but as the prevalence of atypical femoral fracture is very low in the measured population, these results may be skewed by the prevalence of AFF in the patient population scanned [256] . A much larger sample size would be required to ascertain more accurately the prevalence of AFF, perhaps in a more targeted population such as those patients who have been on bisphosphonates for more than three years, with concurrent chronic glucocorticoid use, which has been identified as increasing the risk of AFF [257].

The scan software has been demonstrated to regularly misidentify peaks in the femoral cortex through incorrect automated positioning of cortical edges by the software, and supported by visual assessment of scans to confirm that this is false positive. Visual assessment is carried out by the operator at scan acquisition and also by the individual writing the scan report, whether this is a specialist radiographer or a medical professional. The lateral femoral cortex is examined from the level of the intertrochanteric line to the distal femoral shaft for anomalies or inconsistencies, with the recommendation that a comment is made on the scan report of whether the femur appears normal to the viewer.

Caution should be applied to the misidentification of peaks by the scan software, as patients have not been sent for formal imaging to confirm or deny this. If the software was used as the only basis for investigation of patients with

peaks greater than one millimetre, this would have led to approximately 600 patients per annum being worried unnecessarily, additional pressures being placed on imaging services and a drain on NHS resources. Based on the departmental feedback collected, GE agreed to investigate the issue alongside scan images and technical data, and have indicated a version upgrade will be provided of the current software in an attempt to reduce the likelihood of this occurring. This was due to be released in 2020, however, in light of Covid-19 pandemic, the upgrade has been delayed indefinitely. In summary, there is a requirement for all scans to be visually assessed in conjunction with the scan assessment criteria in appendix 9.12 and the automated scan analysis, as already indicated reliance on the scan software would lead to over investigation in a huge amount of cases.

### 6.4 Beaking index measurements in clinical practice.

The software allows visualisation of the length of the femur, the purpose of this being primarily to measure the thickness of the lateral femoral cortex. Benefits of this are the ability to identify irregularities of the femoral cortex measuring more than 1mm, allowing investigation using x-ray where appropriate. The observation of scans is very subjective, and relies on sufficient training and experience to differentiate between software generated peaks and those which are genuine abnormalities of the femoral cortex.

Beaking index measurements were collected in duplicate, however there is no data available in the published literature of similar works to provide a comparison. The bench testing data from phantoms provided by GE Lunar is

the only comparator available, and as this does not measure differences on a human population, caution should be exercised on direct comparisons. Human tissue is mobile, and moving patients between scans causes a tissue distribution change, leading to inevitable differences between pairs of scans acquired as part of the in-vivo study, identified as especially relevant in patients who are overweight [258].

This may go some way to explaining the anomalies found between beaking index measurements in three patients in which a beaking index difference was found to be greater than 1mm, as two of three of these patients had the highest measured BMI in the study group. Evidence from other studies suggests that BMI is known to influence precision of DXA scanning [258, 259]. The third duplicate scan with measurement difference >1mm had a BMI within normal range, but on examination of the femoral cortex it was found the software had incorrectly identified the cortical border on one scan, and correctly on the other; this emphasises the requirement to visually assess the femoral cortex of all scans, as the automated measurements are not consistently reliable.

It was found that the vast majority of the peaks identified by the software were false positives created by incorrect positioning of the cortical border, equating to around 20% of all scans performed. On initial use of the software, these peaks were all flagged to the reporting consultant, who then had to study each individual and report accordingly. Almost all of these scans demonstrated peaks which were clearly created by incorrect cortical identification by the software, as seen in figure 5.1. It was agreed on software installation that initially all scans demonstrating peaks >1mm should be referred to the reporting consultant, regardless of the BMD measurement. Most of the scans with peaks >1mm had no suspicious features, therefore those with a normal BMD could

have been reported by the radiographer performing the scan, as per departmental protocol. This had the consequence of adding to the reporting burden of the consultant, creating a backlog. All radiographers are now trained and confident to perform the initial visual assessment of the extended femur scans and identify those where the software has incorrectly positioned cortical borders, minimising the number of scans which are sent for consultant reporting.

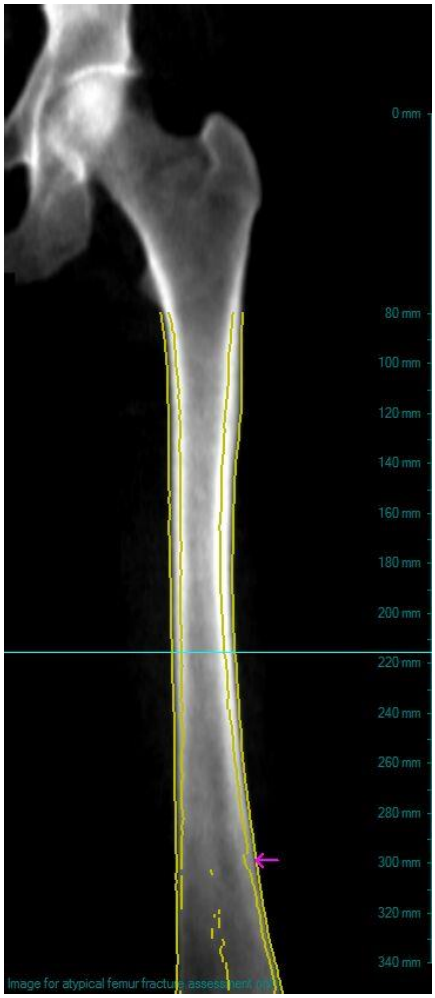



Figure 6.1 A DXA scan with software inaccuracy in identifying the endosteal cortical border of femur.

When this was raised by the reporting consultant, additional training was undertaken to demonstrate the differences between true beaking and software-manufactured false positives. This involved viewing scans obtained within the

department, having asked all operators to note details of scans where they felt there were peaks which may be suspicious, those which they felt were false positives, comparing and discussing with the reporting consultant who gave her assessment on the peaks. This allowed explanation of which peaks were considered suspicious and why, also giving detailed explanation regarding peaks on scans with no suspicious features, and how the groups could be separated. It was also emphasised that if anyone found anything they felt was a true positive, that it should be raised with one of the rheumatology consultants at the first opportunity to allow prompt investigation. These suspicious areas should be identified on the lateral femoral cortex below the level of the lesser trochanter, and the full length of the femur should be assessed for raised areas, peaks, pimples, a dark transverse line emanating from the lateral periosteal border or any other anomaly. This can be observed at scan acquisition and discrepancies examined later at leisure before making a decision on whether any suspicion remains. Discussion of suspicious or unusual cases with colleagues is also beneficial, sharing opinions and knowledge allows further development of general knowledge surrounding both the software and AFFs.

Although not formally audited or assessed, this additional group discussion has resolved the reporting issue in the main, although there are still occasional scans being sent for consultant reporting that could have been reported by radiographers.

The reanalysis of scans as part of the software assessment identified no change in the beaking index measurement in any of the scans, allowing the

operator to be confident that beaking index figures will not alter with scan reanalysis.

When the data transfer from paper to electronic database was undertaken, some gaps in the data were found, along with some inconsistencies in recording patient CHI numbers. When this was identified, all staff were reminded to double check their data, however one radiographer remained inconsistent in CHI number recording throughout the data collection period. This was identified at the time of data input and corrected where possible, to allow the subsequent matching of scan result data and patient demographic data sets.

### 6.5 Staff engagement.

Some staff development issues were highlighted during the process. These included initial staff buy-in of the extended femur scanning software, where there was a lack of awareness of the purpose of the software. A short informal training session at each workstation was held with the GE engineer at the time of software installation. This updated operators on the differences in the centring and scan starting point for the extended femur scan, minor changes to the screen prompts, and to emphasise that no change was required to the routine positioning for femur scanning. A brief background was given on the purpose of the software, how the software worked to identify suspicious peaks on the lateral cortex of the femur using automated measurements, the information provided in the new AFF tab and what the internal process of raising concerns with the departmental manager/consultant reporting on any suspicious peaks. Following a short period of use, there were found to be several issues

surrounding the use of scan software, patient preparation, positioning and scan start points.

The first issue raised was resistance to the new software, as the scan time was extended. In real time, the extended femur scans, if performed bilaterally, resulted in a maximum additional scan time of 114 seconds. This caused some feelings of anxiety, especially in the initial period as operators familiarised themselves with slight alterations to scanning a much longer scan field. Some operators reported difficulty in positioning the shaft of femur centrally in the field of view, while also having to include the acetabulum at the proximal end of the scan. This resulted in the termination and restarting of the scan in an altered position, which lengthened the scan time, however operators conceded that with further use and experience, it became much easier to estimate the position of the acetabulum in relation to the femoral shaft, thereby minimising the requirement to reposition and repeat the scan.

A specific issue was identified in one scan centre, where the operators repeatedly included the patella in the scan field, despite the clear instruction given that the patella was a centring point for the scan field, not an inclusive part of the scan. One operator understood this to mean the patella was being missed off the scan as a software flaw, and started all scans at a lower point deliberately to include the patella. The same operator insisted that a colleague should be doing the same, and it was only when this difference of opinion was raised among all operators that the issue came to light. Agreement was shared among all operators that the patella was a centring point only, not for inclusion in the scan field. This was assessed by a later audit, which found that 28/30 scans were compliant in the elimination of patella and supracondylar flare from the scan field. It became apparent that following the audits and informal training

sessions, some operators were still uncertain how to position patients for the extended femur scans, and began to adapt technique inappropriately to include patella in the scan field. The scan software gives on screen instructions on positioning for each scan, ensuring a common initiation point at the patella, from where the software will calculate a start point for scanning. It was also established that where a patient may be able to slip trousers below the hip area for a scan previously, this was no longer feasible. The trousers would have to be moved to below the knee to give full clearance for the scan, which in turn reduced the degree of femoral abduction that was achievable. For this reason, one operator felt that it would be more appropriate to omit the use of the foot positioner rather than to ask the patient to change their clothing. The reason cited for this was lack of time to change the patient and perform the extended femur scan. This resulted in protocol deviation and potentially leading to confusion and complication should the patient require follow up scanning, where it would be virtually impossible to recreate the original scan position. These scan deviations could be considered as teething troubles, however they may also indicate a requirement for a more formal training structure as initial training was ad-hoc and brief – no other scan centres in Scotland are utilising the software, and there is little practical experience in the knowledge and use of the software to refer to. The applications specialist had no personal practical knowledge of the extended femur scan software, therefore all her training was theoretical, and relied on the supply of images of false positives and true positives from our department to discuss and also to feed back to GE.

When these issues came to light, a further training session was organised on a one-to-one basis with the operator who was deemed to have the greatest knowledge of the scan software and of iAFF/AFF, where staff were observed

scanning a routine patient clinic list, and suggestions made to improve practice, aid the analysis of scans acquired and explain the value of the extended femur scan, as well as answering any questions raised. The additional time taken to complete the extended femur scan was identified as causing anxiety with some radiographers, especially those who were trying to include patellae in the scan field. Once satisfied that this was not necessary, and further practical supported scanning experience using the extended femur scanning software was gleaned, protocol was adhered to and scan quality improved to previous levels. It may also have been beneficial to have the GE applications specialist present when the software was initially used to ensure a structured approach to training in the new elements of the scan process, although the benefit may have been insignificant as she had little practical knowledge of the software and the provision of scan images may aid the software development in future.

Following these issues, it was agreed that a face-to-face professional development meeting of all operators would allow all concerns to be raised and shared, reiterating the importance of the new protocol and what the software was looking to identify.

Highlighted issues:

1. Removal of inappropriate trousers is a necessity, rather than pulling down past hip area.
2. Relevance of beaking/peaks identified on scan.
3. Differentiation of true peaks and those manufactured by software – with some examples of software created peaks.
4. Asking patients about groin/thigh pain that doesn't go away.

5. The importance of identifying anything thought to be a true positive as soon as possible with the reporting consultant to allow review.

These issues were resolved with in-house training sessions on a one-to-one basis, which allowed each person to ask questions and seek support based on their own needs. This took place during a clinical scan list, allowing demonstrations of good technique and best practice with scan positioning and analysis.

Explanation was made of the relevance of prodromal pain, which has been linked in numerous studies as an indicator of AFF, indeed it is one of the minor criteria for AFF specified by the ASBMR[199]. Prodromal pain was reported to affect almost 90% of study participants in a small retrospective study of nine AFF sufferers in India [98], however other studies have reported a much lower level of prodromal pain among participants, reported as 27% in a larger, longer running study of 86 patients [76]. Both studies agree that the sample size is small, but there is recognised difficulty in large scale recruitment for a rare condition. Until the software was installed, no consideration was given to asking patients whether they had any prodromal pain. This was addressed during the 6 month data collection, where every patient was asked if they had any groin pain. Further to this, it is intended that the question be asked of each patient at every scan appointment, and the response recorded on the patient questionnaire. In practice, this is not always recorded, in some cases it will only be recorded if the patient gives a positive response.

Supplementing this, an applications specialist from GE spent a day with all staff running through the advanced software applications, emphasising the need for consistent and reproducible positioning, scanning and analysis in the precision

of serial scanning, which all felt aided in their understanding of the software processes and measurements. A further audit of scan positioning and analysis is planned for 2020, which will give an indication of levels of compliance with training and development as previously delivered, however this has been postponed as scanning activity has been halted due to Covid 19 pandemic.

### 6.6 Service recommendations.

Several points for service development have been identified: lack of formal training in the use and evaluation of extended femur DXA scanning software, audit of scans, development of a formal training structure for extended femur scans, ongoing staff development in the identification of both true and false positive scans and the creation of an image set of scans as a reference base for future staff training and development.

The auditing of positioning and technical analysis of extended femur scans should become routinely embedded in clinical practice, to be performed every three months, aiding the identification of any deviation from best practice and to identify ongoing training or support needs.

At present there is no formal training structure available for the practical use and application of extended femur DXA scanning. The ad-hoc nature of the training provided by GE at software installation allowed for slight differences in practice between operators, with no in-depth practical training or demonstration available. The lack of practical use of the software by the engineer or the applications specialist meant they were unable to resolve some of the queries raised initially, and learning about the software was on a trial and error basis. A

more formal training structure with recorded supervision may aid the elimination of differences in practice between operators, therefore improving consistency in scanning practice and analysis.

Especially relevant to this would be the ability to identify false positives, based on scan presentation and the positioning of cortical borders placed by the scan software. Some images in which the software appeared to misjudge the femoral cortex were anonymised and sent on to GE software developers in Europe for analysis as a basis for modifications to the software program.

A compilation of images with irregularities and anomalies could be gathered and used as a basis for training and development, presenting images with both true and false positive peaks would allow operators to become more familiar with the visual appearance of peaks on images, and differentiating between real peaks and software generated peaks on DXA scan images. The reference images found online for AFF and iAFF were all from radiographs or other imaging modalities, not extended femur DXA scans using the GE Lunar software package.

## 6.7 Limitations of this work.

Several limitations of this study have been identified. The predominant ethnicity of the study area is Caucasian, as are the vast majority of all patients scanned. This affects the transferability of results across populations which are ethnically diverse. It has been identified in several research papers that those at increased risk of AFF are of Asian ethnicity.

There has been no identification of false negative extended femur scans in the short term, however this may change in future with prolonged use of the scan software. There may be the possibility of missing an iAFF at the proximal femur around the area of the gluteus insertion point, where cortical thickening may be missed, or conversely a prominent muscle insertion may lead to over investigation.

All the audits and precision study undertaken directly for this study have been reliant on small sample sizes, which limits the statistical power, and should be repeated on larger sample size to improve this.

When assessing ten year data for potential AFFs, not all radiographs were reviewed, therefore some cases may have been missed. As a consequence of this, the percentage quoted may under-represent the actual numbers of individuals affected by AFF in the time period, due to the absence of orthopaedic arbitration data. Lack of patient notes and the relative inexperience of the retrospective reviewers in assessing images for AFF may also be potential weaknesses of this work.

The lack of ICD coding specifically for AFF has also been identified throughout literature as a barrier to clear identification of AFF, as have incorrectly coded

fractures. The number of patients found with AFF identified from NHS Grampian health intelligence data may under-represent the actual numbers of AFF as several issues were found with missing or inaccurate ICD coding in common with several other studies examining AFF [5, 32, 153, 200]. Other confounding factors were non-specific wording of imaging reports and failure to identify AFF being a differential diagnosis.

# 7 Conclusion and future research.

This section summarises the conclusions of the studies undertaken, along with some recommendations for extending this work in the future.

## 7.1 Conclusions.

The precision study undertaken provides reassurance that total hip and femoral neck BMD measurements are not adversely affected by the use of the new software with scanning using the extended femur option. The precision errors for the beaking index were much greater than those for BMD measurements from the same study. The beaking index precision errors are above acceptable limits and underpin the recommendations made in this thesis for visual assessment of identified beaks without over-reliance on the software.

The study explored the ability of the analysis software to accurately identify beaking. The software made errors in 20 percent of the population and created what have been termed as false peaks, characterised as those peaks artificially created by the scan software. It is recommended that the impact of false peaks can be minimised through visual assessment of the scan images in conjunction with the software measurements. False positive peaks on scan images cannot be conclusively defined as such without further formal radiographic imaging, therefore reliance on the scan software alone would lead to over investigation in around a fifth of DXA scans performed in an adult population. Visual inspection of the lateral femoral cortex has been demonstrated to be more effective than the software assessment, and should be undertaken as first line of

investigation, in addition to the use of the software assessment of the femoral cortex within the scan software. As a consequence of the findings of this study, it may be prudent for GE to consider adding a warning to the extended femur scanning software both on the packaging and on installation/use alerting users to the requirement for visual assessment of scans in conjunction with the software assessment, especially if an automated report is produced highlighting the beaking index measured on the extended femur scans. Specifically, abnormalities should be below the level of the trochanters, as documented by the ASBMR criteria [199], and consideration given to the lateral cortex of femur only. Any raised area, peak, pimple or dark line should be assessed and considered in conjunction with the AFF software tab. This should take place during scan acquisition and also at the time of scan reporting, and a statement should be made on each report on findings of the extended femur scan, even if entirely normal.

Based on the evidence available on the finding of AFF and iAFF in patients who are bisphosphonate naïve, it may be prudent to consider scanning all patients over the age of 40 years using the extended femur scanning software. There is little evidence of AFF occurring in patients below the age of 50 years. To date no iAFF or AFF have been seen on extended femur scan patients in NHS Grampian who are bisphosphonate naïve or aged under 50 years, however the baseline scans being undertaken now provide a serial record of the femur, identifying any abnormality within the lateral femoral cortex, allowing monitoring and planned intervention prior to a fracture occurring. Prophylactic nailing has been indicated as reducing patient recovery and healing time, pressure on traumatic orthopaedic services is minimised from this area and has a cost saving to the NHS in terms of inpatient recovery times.

The average incidence of AFF in NHS Grampian over a ten year period was 0.18% of all femoral fractures in patients aged 50 years and older, with all patients being of Caucasian ethnicity and having bisphosphonate exposure in keeping with a similar UK study [242]. The majority of these patients were female, with a mean age of around 75 years, and the bulk of the fractures were classified using ICD 10 coding as subtrochanteric.

Training in the use and application of the extended femur scanning software should be considered as two phases; initial and ongoing, with audit suggested within three months of installation to ensure any digressions from gold standard positioning and scan technique are identified and addressed. The lack of a formal training package from GE on the background and clinical use of the extended femur scan software was identified as a drawback in the initial use of the software program in a routine clinical DXA scan environment. The ongoing training should include education around muscle insertions, which may cause peaks on scanning, but are not considered suspicious, and the presentation of false positive peaks. The lateral cortex of the femur should be visually assessed from below the level of the trochanters to the supracondylar flare on each scan acquired, and any suspicious areas of cortical thickening or beaking highlighted. Auditing of positioning and technical quality of extended femur scans should be repeated on a quarterly basis to ensure continuity and quality are maintained. This is especially relevant when new operators are introduced, or where scan equipment or software is upgraded.

Additional time taken for scans is minimal, but in the advent of service redesign and waiting times management post Covid-19 pandemic, this may be an area of cutback due to time pressures. If this is the case, recent moves toward empirical treatment with bone strengthening medications based on age, fracture

site and concomitant medications as recommended by the SIGN guidelines [29] may lead to over-treatment, risking a future increase in iAFF and AFF.

## 7.2 Future research.

There has been no investigation of false negative extended femur DXA scans in clinical practice, classified as patients who have no indication of peaks/irregularity on extended femur DXA scan who subsequently suffer an AFF. As AFFs are rare events, and the extended femur scan software has only been in clinical use for a short time, no false negative scans have been identified. This may change in the longer term, and a study of false negatives may only be possible in a large scale, multi centre study including many thousands of patients and DXA scans, which is outwith the remit of this small scale research.

A large scale in-vivo precision study encompassing all operators and scanners associated with the department would add statistical power to the work already completed, provide ongoing quality assurance and ensure consistency throughout the department. This work would be valuable in assessing the LSC of newer members of staff, who have not yet had this assessed; particularly relevant as two operators have retired and been replaced in the process of this research study.

There is no formal education or training structure available for the use and evaluation of extended femur DXA scanning, and it may be valuable to develop

a short core training module which introduces the software, its uses in a clinical setting and evaluation of the scans acquired. With the addition of DXA scan images of software and bone irregularities, true and false positives and descriptions, this could provide a resource for operators to refer to for reference purposes and continuing development.

It may be prudent to devise and refine a set of criteria specifically for the assessment of false negative scan peaks, which operators can use to check scans as they are acquired. There is also the possibility of then re-auditing some areas of technical assessment, positioning and scan analysis to measure any change in operators and viewers perception of images.

As the duration of software use increases, the use of DXA may aid the identification of pre-existing defects within femoral shaft, and measurement can be made of cortical thickening, allowing monitoring of serial scan data to predict iAFF. The collection of iAFF data from DXA and AFF on radiographic imaging over a specified time period would allow comparison of iAFF and AFF rates in parallel.

There are various studies of genetics and osteoporosis, an area still in its infancy, and it may be valuable to perform gene sequencing using samples obtained from patients with iAFF as a further study route in identifying genes which may be associated with AFF.

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# 9 Appendix section.

## 9.1 Patient information sheet



Participant Information Sheet

**Title of Project: Short-term precision study of dual energy x-ray absorptiometry (DXA) bone density scanning of the extended femur scan for atypical femoral fracture in routine clinical population.**

**Chief Investigator: Karen Knapp**

**Invitation and brief summary:**

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to consider the information carefully and to discuss it with GP, family or friends if you wish. Please ask the researchers any questions that you may have.

Measurement of bone mineral density (BMD) by DXA scanning is routinely used to diagnose osteoporosis (thinning bones). It also measures how well treatments are working. When we compare scans it is important to be able to tell the difference between real changes in you and those made by measurement process itself. This is known as the reproducibility (precision) of measurements.

This is an extension of our current scanning software and because it hasn't been used by us before, we don't know how reproducible these measurements are. We would like to test this by scanning your thigh bones twice, with you getting up of the scanning couch between scans. We want to see if there is any change is between two scans of your whole femur bone. We can do this by comparing scans of 30 patients aged 20 years and over.

Anyone referred for a DXA scan at Ashgrove House, Foresterhill, Aberdeen could be asked if they would like to take part in the study. Routine care means having one DXA scan of the lower spine and extended femur (thigh bone). We want to see if there is any change in the measurement precision between two scans of your thigh bone. Each person who participates in the study will receive an additional scan of both thigh bones.

Appointment times are 30 minutes long and one visit only. There is no further follow-up except for your routine clinical care.

It is sometimes necessary to compare our scan measurements over time. This helps doctors to decide whether to start or stop treatment. When we compare these scans it is important to decide between real changes in a patient and those

changes related to the scan process. This includes the reproducibility (precision) of measurements taken.

The skill of the radiographers performing the scans affects the precision of the measurements. Their ability to position a patient for the scan is the biggest source of change. A test of this is best made by scanning a sample of people, in this case 30. This allows us to tell more accurately if the changes we see in the femur bone are significant. This is important to make sure we are provide all our patients with the best possible care.

**Purpose of the research:**

The aim of this study is to determine the precision error, or reproducibility, for measuring the outer edge of the femur bone. This will help ensure best care for patients attending Grampian Osteoporosis Service, and will form part of an educational award for a Masters degree in Medical Imaging.

**Why have I been approached?**

We are inviting all patients over the age of 20, who have not had both hips replaced to take part. If you have had both hips replaced you will not be able to participate.

**Do I have to take part?**

No, it is up to you to decide whether to take part. If you decide to take part, you are still free to withdraw at any time without giving a reason. A decision to

withdraw at any time, or a decision no to take part, will not affect the standard of care you receive.

**What would taking part involve?**

Taking part would involve a second extended femur scan being done at the same time as your routine appointment. You would need to get up from the scanner and then lie down again between scans. No additional time or further visits are required. If you decide to take part, you are still free to withdraw at any time and without giving a reason. If you do not want to take part, or change your mind, you will still receive the bone density scan requested by your doctor, but the second scan will not be carried out. This will not affect the standard of care you receive now or in the future. Everything else done during the appointment is part of standard clinical care. This is described in the scan information leaflet sent out with your letter.

**What will I be asked to do if I decide to take part?**

You will attend for the bone density scan requested by your doctor at the time and date stated in your appointment letter. You may be asked by the radiographer if you wish to take part in the study. If you agree, you will be asked if you have read and understood this information sheet. You have the opportunity to ask any further questions. You will then be asked to read and sign a consent form, you will get a copy of this too.

When you attend for your appointment, the radiographer will check your name, date of birth, and address with our records. Your height and weight will be measured. We will chat about the details of the 'osteoporosis questionnaire' that you received in the post with your appointment letter and the answers entered into the DXA computer.

You will be asked to lie flat on a firm couch whilst the arm of the scanner passes over you to take the images. It does not involve going into a 'tunnel' or having an injection. The areas routinely scanned are the lower back and extended femur.

The lower back and extended femur scan are performed as routine care. After this first scan, you will be required to come off the scanning table and back on again to be repositioned for the second study scan of the extended femur.

The scan appointment will take approximately 30 minutes and the extra extended femur scan will be done during your routine clinical appointment. You will not be required to attend for any further appointments as part of the study.

**What are the possible benefits and disadvantages of taking part?**

The study has no immediate benefits for you. Your participation will help us understand how extended femur measurements taken on our scanners may differ. It will also help us to know what the reproducibility (precision) of these measurements is. This enables us to more accurately report changes over time. This can inform important decisions such as stopping or starting treatment.

If you take part in this study you will have an additional scan of your extended femur performed. This will be extra to those that you would have if you did not take part. This procedure uses ionising radiation to form images of your body

and provide clinical information. Ionising radiation can cause cell damage that may, after many years or decades, turn cancerous. We are all at risk of developing cancer in our lifetime. The normal risk is that this will happen to about 50% of people at some point in their life. Taking part in this study will add only a very small chance of this happening to you. To put this risk into perspective it is approximately the equivalent of several days background radiation or eating 2 bananas.

**What will happen to the results of my bone density scan?**

The bone density scan performed as part of your routine clinical care will be reported in the usual way and a copy of the report sent to your GP and filed electronically in your medical notes. The extra extended femur scan taken as part of the study will be stored in the usual way alongside the first scan. The extended femur measurements from these scans will be used as part of the study.

**What will happen to the results of the study?**

They will be presented at conferences and written up in journals and publicly available for you to see on the University of Exeter website https://ore.exeter.ac.uk/repository. Results are normally presented in terms of groups of individuals. If any individual data are presented, the data will be totally anonymous, without any means of identifying you as an individual and to protect your confidentiality.

**How will my information be kept confidential?**

The University of Exeter is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Exeter will keep identifiable information about you for 5 years after the study has finished. There will not be any transfer of identifiable patient data between NHS and Uni.

Due to recent regulatory changes in the way that data is processed (General Data Protection Regulation 2018 and the Data Protection Act 2018) the University of Exeter's lawful basis to process personal data for the purposes of carrying out research is termed as a 'task in the public interest'. The University will endeavour to be transparent about its processing of your personal data and this information sheet should provide a clear explanation of this. If you do have any queries about the University's processing of your personal data that cannot be resolved by the research team, further information may be obtained from the University's Data Protection Officer by emailing dataprotection@exeter.ac.uk or at www.exeter.ac.uk/dataprotection. If you have any concerns about how the data is controlled and managed for this study then you can also contact the Sponsor Representative, Pam Baxter, Senior Research Governance Officer, whose details are at the end of the information sheet.

We will collect your name, address and contact details and information about any relevant clinical conditions, medication and additional personal data such as date of birth, weight, height and the data generated from the tests. We will store them

securely in the study files and on an encrypted University of Exeter laptop, and scan data on our encrypted NHS scanning computers. The files will be protected in a locked room within the DXA department with only research team having access. The building which houses all the research data is security protected by the NHS. When the data is stored the name and addresses will be removed from the data so that it can be identified only by an ID code (pseudonymised) and the data will be stored for no more than 10 years. This pseudonymised data will be shared with staff at the University of Exeter. When the results of the study are analysed individual participants will not be identifiable in order to protect their confidentiality. The data will be accessed and analysed only by the researchers, the supervisors of the research and research auditors. You are welcome to request a copy of the results of the project. With your consent, we will inform your GP that you have taken part in this research.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

**Who is organising and funding this study?**

This study is sponsored by the University of Exeter, no funding is required.

**Who can I approach if I have a complaint about this study?**

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Their contact

details are shown below. If you remain unhappy and wish to complain formally, you can do this via the NHS Grampian feedback service based at Summerfield House. They can be contacted on 0845 3376338.

**What will happen if I don't want to carry on with the study?**

You can stop taking part in the study at any time without giving a reason and without any disadvantage to yourself of any kind. If you decide that you wish to stop taking part in the study then all of your research data and any personal data that has been collected in order for you to participate will be securely destroyed and will not be used in any write up or publication about the study. Once the data has been anonymised and published it will not be possible withdraw any individuals data.

**Will I receive any payment for taking part?**

No payment will be made to participants.

**Who is organising and funding this study?**

This research is being Sponsored by University of Exeter and supervised by Prof Karen Knapp.

**Who has reviewed this study?**

This project has been reviewed by the North of Scotland research Ethics Committee (1) and NHS Grampian R&D.

**Contacts for further information**

If you have any questions or would like some more information about the study, please do not hesitate to contact us:

| | |
|---|---|
| Mrs Diane Smith<br>Specialist Radiographer<br>Grampian Osteoporosis Service<br>Ground Floor<br>Ashgrove House<br>Aberdeen Royal Infirmary<br>Aberdeen, AB25 2ZN<br>**Tel: +44 (0) 1224 550820**<br>**Email: diane.smith26@nhs.net** | Dr Rosemary Hollick<br>Consultant Rheumatologist<br>Grampian Osteoporosis Service<br>Ground Floor<br>Ashgrove House<br>Aberdeen Royal Infirmary<br>Aberdeen, AB25 2ZN<br>**Tel: +44 (0) 1224 559978**<br>**Email:rhollick@abdn.ac.uk** |

If you wish to talk to someone who is independent of the study team, please contact Ruth Garside 01872 258148.

If you feel your treatment either prior to, during or after the study is of concern to you in any way, or if wish to complain, please contact the supervisor for the research, Dr Karen Knapp on 01392 264133.

If you have any questions related with Ethical concerns or data management, please contact the Research Ethics and Governance Office of the University of Exeter. The **Sponsor Representative** for this study is Pam Baxter, Senior

Research Governance Officer who can be contacted by e-mail p.r.baxter2@exeter.ac.uk or Tel: 01392 723588.

**Thank you for your interest in this project.**

## 9.2 Patient letter

Grampian Osteoporosis Service

Ground Floor

Ashgrove House

Aberdeen Royal Infirmary

Aberdeen, AB25 2ZN

Tel: +44 (0) 1224 550820

Email: diane.smith26@nhs.net

[Date]

Dear [Recipient Name]

Invitation to take part in a research study/service evaluation

**Short-term precision study of extended femur scans using DXA scanners in routine clinical practice.**

We are looking to recruit 30 volunteer patients to help us complete this study. You are invited to have a second extended femur (thigh bone) scan, in addition to the scan you are scheduled to attend for. This will be undertaken during the same appointment, lasting around 30 minutes in total. Dual Energy X-Ray Absorptiometry (DXA) is currently the most accurate and reliable method used to measure bone density and is a simple and painless procedure.

This study will help us to understand if the changes we see in a patient's measurements are real, or simply represent the fluctuations in the measurement itself due to differences in the scanning technique of our radiographers. It will help us more accurately report changes in bones when comparing scans over time. This can inform important decisions such as stopping or starting treatment.

Further information about this, and about the study, are included in the participant information sheet accompanying this letter. If you do not wish to participate it will have no effect on the care you receive, you should still attend for the appointment you have been sent. If you are interested in taking part in this study, please let the radiographer know when you attend for your appointment. Thank you.

Yours sincerely

Diane Smith (Principal Investigator/Specialist Radiographer)

## 9.3 Patient consent form In-vivo precision study

Study ID number of participant:

**CONSENT FORM**

**Short-term precision study of dual energy x-ray absorptiometry (DXA) bone density scanning of the extended femur scan for atypical femoral fracture in routine clinical population.**

Chief Investigator: Karen Knapp

**Please initial box**

1. I confirm that I have read and understood the information sheet (version 1.1 dated 2nd December 2019) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactory. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected, either now or in the future. ☐

3. I understand that data collected during the study may be looked at by individuals from the University of Exeter, regulatory authorities or from the NHS Board/Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that taking part involves anonymised clinical data from my DXA scan being used for the purposes of this research study. ☐

5. I understand that the anonymised data will be securely stored for 10 years after the study has ended. ☐

6. I understand that the anonymised data from the study may be used for presentations and publications. ☐

7. I agree to take part in the above study. ☐

8. I agree to being contacted by post or email with a summary of the findings of the study, at the address I have provided below. ☐

| _____ | _____ | _____ |
|---|---|---|
| Name of participant | Date | Signature |

| _____ | _____ | _____ |
|---|---|---|
| Name of Researcher taking consent | Date | Signature |

When completed: 1 copy for participant and 1 copy for researcher/project file

## 9.4 Protocol



**FULL/LONG TITLE OF THE STUDY**

Short-term precision study of dual energy x-ray absorptiometry (DXA) bone density scanning of the extended femur scan for atypical femoral fracture in routine clinical population.

**SHORT STUDY TITLE / ACRONYM**

Short term precision of extended femur scans using DXA.

**PROTOCOL VERSION NUMBER AND DATE**

- Version 1.0 8th November 2019

**RESEARCH REFERENCE NUMBERS**

**IRAS Number:** 259999

**SPONSORS Number:** 1819/42

This protocol has regard for the HRA guidance

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

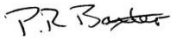
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

**For and on behalf of the Study Sponsor:**

Signature: Date:

07/11/2019



Name (please print): Ms Pam Baxter

Position: Senior Research Governance Officer

**Chief Investigator:**

Signature: Date:

..... ...../...../.....

Name: (please print):

Karen Knapp

LIST of CONTENTS

KEY STUDY CONTACTS

| | |
|---|---|
| Chief Investigator | Professor Karen Knapp, University of Exeter, South Cloisters, Heavitree Road, Exeter. K.m.knapp@exeter.ac.uk. 01392 724133. |
| Study Co-ordinator | Diane Smith, Specialist Radiographer, Grampian Osteoporosis Service, Ashgrove House, Aberdeen AB25 2ZA. 01224550820. Diane.smith26@nhs.net |
| Sponsor | University of Exeter<br>Sponsor Representative<br>Ms P Baxter, Senior Research Governance Officer, Research Ethics & Governance Office, Lafrowda House, St German's Road, Exeter, Devon<br>EX4 6TL.<br>01392 723588<br>p.r.baxter2@exeter.ac.uk |

**STUDY SUMMARY**

| | |
|---|---|
| Study Title | Short-term precision study of dual energy x-ray absorptiometry (DXA) bone density scanning of the extended femur scan for atypical femoral fracture in routine clinical population. |
| Internal ref. no. (or short title) | Short term precision of extended femur scans using DXA |
| Study Design | In vivo precision study. |
| Study Participants | Patients >20 years routinely attending for DXA scanning at Grampian Osteoporosis Service at Ashgrove House, Aberdeen Royal Infirmary |
| Planned Size of Sample (if applicable) | 30 participants |
| Follow up duration (if applicable) | None |
| Planned Study Period | 9 months |
| Research Question/Aim(s) | The aim of this study is to determine the precision error, or reproducibility, for measuring the outer edge of the femur, found using extended femur scan software as part of a routine DXA scan procedure |

**FUNDING AND SUPPORT IN KIND**

| **FUNDER(S)**<br>(Names and contact details of ALL organisations providing funding and/or support in kind for this study) | **FINANCIAL AND NON FINANCIALSUPPORT GIVEN** |
|---|---|
| **NHS Grampian** | **Administrative support** |
| **University of Exeter** | **Sponsor** |
| | |

**ROLE OF STUDY SPONSOR AND FUNDER**

This research is being sponsored by the University of Exeter and supervised by Dr Karen Knapp.

Role of Sponsor

The study sponsor will ensure that the research team has access to resources and support to deliver the research as proposed and that responsibilities for management, monitoring and reporting of the research are in place prior to the study commencing. The sponsor will ensure that there is agreement on recording, reporting and reviewing significant developments as the research

proceeds and approve any modifications to design, obtaining requisite regulatory authority.

The sponsor will assume responsibility for operating the management and monitoring systems of the research.

Prior to the study commencing the sponsor will be satisfied that:

- The research will respect the dignity, rights, safety and well-being of participants and the relationship with healthcare professionals.
- Where appropriate the research has been reviewed and approved by an NHS Research Ethics Committee and/or the Health Research Authority Approval Programme.
- The Chief Investigator, and other key researchers have the requisite expertise and have access needed to conduct the research successfully.
- The arrangements and resources proposed for the research will allow the collection of high quality, accurate data and the systems and resources will allow appropriate data analysis and data protection.
- Organisations and individuals involved in the research agree the division of responsibilities between them.
- Arrangements are in place for the sponsor and other stakeholder organisations to be alerted to significant developments during the study, whether in relation to the safety of individuals or scientific direction.
- There are arrangements for the conclusion of the study including appropriate plans for the dissemination of findings.

The sponsor plays no role in the design of this study, and will have no role in data analysis or interpretation, or writing up of findings of the study.

**PROTOCOL CONTRIBUTORS**

- Contributors to the protocol are Dr Karen Knapp, Dr Chris Wright, Dr Rosemary Hollick and Diane Smith.

**KEY WORDS:**

Osteoporosis

Atypical femoral fracture

Bisphosphonates

Extended femur scanning

DXA scanning

STUDY FLOW CHART

| What? | When? | Period of time? |
|---|---|---|
| Patient invitations sent | October/November 2019 approx | 5 weeks approx |
| Study scans | December 2019 – January 2020 | 3 weeks approx |
| Analysis of study data | February 2020 | 4 weeks approx |

**STUDY PROTOCOL**

Short-term precision study of dual energy x-ray absorptiometry (DXA) bone density scanning of the extended femur scan for atypical femoral fracture in routine clinical population.

BACKGROUND

Measurement of bone mineral density (BMD) by Dual Energy X-Ray Absorptiometry (DXA) is the gold standard imaging modality routinely used to diagnose osteoporosis (thinning bones) and monitor response to treatment. When comparing scans it is important to distinguish between real changes in patients opposed to changes related to the measurement process itself e.g. the reproducibility (precision) of measurements.

Interest has arisen in the use of software developed by DXA scanner manufacturers General Electric (GE) Lunar in 2015, which is routinely used during a DXA scan, to identify irregularities on the lateral cortex of the femur. This potentially allows the identification of cortical lesions at an early stage, as part of routine clinical scanning, with no detriment to bone mineral density measurement at the hips[224]). GE have conducted test scans using phantoms with simulated beaking to establish an in vitro precision error margin of 0.5mm, however these phantoms are not available to us to utilise. Phantoms under-estimate the actual precision errors in-vivo because they lack the biological range found in humans. There have been no published studies found that have undertaken precision measurements using this software in a human population. The software incorporates the ability to measure the thickness of the lateral

cortex of the femur, using serial measurements over time to assess change in the cortex.

RATIONALE

The aim of this study is to determine the precision error, or reproducibility, for measuring bone cortex of the outer edge of the femur bone using human subjects as described above. This will help ensure best care for patients and develop further resources within the medical imaging community. It will also form part of an educational award for a Master's by Research degree in Medical Imaging.

RESEARCH QUESTION/AIM(S)

The aim of this study is to determine the precision error, or reproducibility, of the scanner for measuring the outer edge of the femur and any identifying any areas of thickening. Thickening, or "beaking" is classified as an area of thickening, occurring on the outer edge of the shaft of femur. This will help ensure best care for patients and will form part of an educational award for a Master's by research degree in Medical Imaging.

**Objectives**

To determine the in-vivo precision error of femur cortex measurements using DXA scan.

STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

We look to recruit 30 participants for inclusion in the study. It is estimated that we will send information to around 75 patients, assuming that approximately 50% of patients will participate. It is suggested that 30 participants be scanned to obtain statistically valid results (Gluer et al., 1995).

All eligible participants will be sent a participant information sheet and a covering letter in addition to their standard clinic appointment letter and osteoporosis questionnaire within the same envelope. These are routinely sent out around 6 weeks in advance.

Each patient will attend for one routine scan appointment, which will be approximately 30 minutes in length.
On the day of the appointment, potential participants will be approached by a suitably qualified member of staff and asked if they have read and understood the information sent out. They will then be asked if they would be willing to participate. Any questions or queries will be discussed. If the patient is happy to participate, consent will be gained in writing, a copy of the completed consent form will also be given to the patient to take away with them.

All participants will have their name, address and date of birth checked with departmental records, measurement of height and weight, and discussion of the

standard osteoporosis department questionnaire with the radiographer in private as part of routine care. These will be recorded in the secure DXA scanner computer, also part of routine clinical care.

The participant will then be asked to lie on the scanner bed, and have scans taken of each extended femur individually, then a scan of the lower spine (three individual scans) as per standard practice. The scanner arm passes over the body and takes images as it does so. This does not involve any injections or going into a tunnel.

After this process, the participant will be asked to rise form the scanner bed, then lie back down. This mimics a patient returning for a second scan and is considered best practice for short term precision scans. A further scan of each extended femur will be taken (two additional scans).
Following this, the participant is free to leave, with no further study follow up required. They will be provided with a clinical diagnosis via the referring clinician as per our standard protocol, but they will not be given precision error results.

Personal data from participants will be identified by the direct clinical care team. The personal data, including scans, of all patients attending the service for a DXA scan are stored on a secure NHS server that complies with NHS data protection, security and confidentiality policies. The additional DXA scan performed as part of the study will be captured and stored in the same manner as routine clinical scans. Only those with appropriate access controls i.e. members of the direct clinical care team will have access to this.

All data collected from the study DXA scans will be pseudonymised. Data of from the extended femur will be collated along with the age range and gender mix of those scans. This will be stored on a secure NHS server. This file will not contain any personal data of participants and will be pseudonymised by means of a unique code, stored on a separate file on the secure NHS server, linking the non-identifiable data to the original DXA.

No identifiable patient data will be transferred from NHS server or outwith the direct clinical care team.

Pseudonymised data will be stored and analysed on a University of Exeter computer by members of the research team, which is password protected and accessible only be the research team.

Consent forms will be kept in the study file, stored in a locked filing cabinet within the Grampian Osteoporosis Service.

The filing cabinet can only be accessed by members of the direct healthcare team. The department has restricted access to authorised personnel via a keycard.

Patients will be assigned a unique identification number. The information that links the ID number to participants' personal data will be kept separately and securely. Hard copies of consent forms will be kept in locked filing cabinet and electronic data kept on a password-protected spreadsheet in the secure NHS Grampian server. The personal data will be kept separately so that only approved staff members of the research team who have need to use personal data will have access to the information linking ID numbers to participants, or the personal data. No patient identifiable data will be reported in research outputs.

All information and data will be handled and processed in accordance with the Data Protection Act 2008 and the General Data Protection Regulation. Pseudonymised data will be analysed by researchers at NHS Grampian and the University of Exeter in Aberdeen under the direction of the chief investigator. Descriptive statistics (mean and standard deviation) to describe the patient population (age, gender, height, weight, body mass index (BMI) kg/m2, beaking measurements, bone mineral density (BMD) in g/cm2, T-scores) and comparison with mean age and gender of standard patient population, calculated from 2018/2019 departmental referral data.

The pseudonymised research data will be archived according to University of Exeter guidelines, and stored as research data for up to 10 years.

STUDY SETTING

Anyone referred for a DXA scan at Ashgrove House, Foresterhill, Aberdeen could be asked if they would like to take part in the study.  Routine care means having one DXA scan of the lower spine and extended femur (thigh bone).

**SAMPLE AND RECRUITMENT**

**Eligibility Criteria**

**Inclusion criteria:**

All patients >20 years routinely attending the Grampian Osteoporosis Service at Ashgrove House, Aberdeen Royal Infirmary, for DXA scan are eligible for inclusion. The request for DXA scan will be made by the referring physician and vetted in the usual way as per local referral guidelines for DXA scanning and IR(ME)R Regulations.

**Exclusion criteria:**

Patients <20 years of age.

Patients unable to give consent.

Patients who have had bilateral hip surgery.

Patients who are pregnant.

**Sampling**

To obtain statistically valid results, multiple determinations of femur scanning are performed for a specific anatomical site e.g. femur. The mean measurements are then determined.

### 6.2.1 Size of sample

It is recommended that precision testing be performed to allow for 30 degrees of freedom to ensure that the upper limit for the 95% CI of the precision error is no more than 34% greater than the calculated value. Since one of the measurements on a specific patient does not contribute independently to calculation of the mean result for that individual, it is recommended to perform 2 extended femur measurements on 30 individuals. It is recommended that precision testing be performed to allow for 30 degrees of freedom to ensure that the upper limit for the 95% CI of the precision error is no more than 34% greater than the calculated value.

### 6.2.2 Sampling technique

To achieve a target of 30 patients > 20 years for each precision study, we will send study information to approximately 75 patients. This assumes approximately 50% of patients will be willing to participate.

## 6.3 Recruitment

All potential participants will be sent a letter and participant information sheet in the post, along with their standard DXA appointment in advance of the appointment. During that time period, patients will have the opportunity to contact a member of the research team if they have any questions or concerns. When they arrive at the clinic they will be asked to confirm whether or not they have read and understood the participant information and whether they wish to

participate when they arrive at clinic for their appointment. Further time will be made available then to clarify any points, provide further information if required and to sign the consent form.  Some patients may inadvertently be sent information regarding the study, but not eligible to take part as may lack capacity to consent, or have bilateral hip replacements.

### 6.3.1 Sample identification

The direct clinical care team (Grampian Osteoporosis Service) will approach potential study participants via a covering letter and participant information sheet (attached) which will be sent along with their standard DXA appointment letter.  This is posted to patients around 6 weeks prior to their appointment.

### 6.3.2 Consent

Patients will be asked to confirm whether they have read and understood the participant information sheet and understand what participation would involve, and whether they wish to participate when they arrive at clinic for their appointment. Further time will be made available then to clarify any points, provide further information if required.

The person seeking consent will then go over the information with the participant again, answer any questions, and if satisfied that they are capable of

consent ask them to sign the consent form.  A copy of the signed consent form will be provided to the patient prior to departure from the department.

Patients will participate in the study for a total of 30 minutes maximum, the majority of this time will be spent receiving standard clinical care. We therefore assume for the purpose of the study that capacity is unlikely to be lost within such a short timeframe and continued capacity for the 30 minute duration of the study will be assumed.

Should a patient not wish to participate, or continue with participation in the study, no reason needs to be given.  It will be made clear there is no detriment to their standard clinical care, and no pressure will exerted to participate in any way.

## ETHICAL AND REGULATORY CONSIDERATIONS

### Assessment and management of risk

Minor intrusion and inconvenience as a result of reading through the patient information sheet, understanding the study information and completing consent form. There is the potential for minimal discomfort in terms of having to physically move off the scanning table and back on again for the additional scan. All participants attending for a DXA scan are required to get onto the table once then off again. All other activities are per standard clinical care (completion of bone health questionnaire, measurement of height and weight). DXA scanning is a very safe test with a radiation burden considered equivalent to a few hours of average natural background radiation in the UK

### **Research Ethics Committee (REC) and other Regulatory review & reports**

Before the start of the study, a favourable opinion will be sought from the Health Research Authority (HRA) REC for the study protocol, consent forms and other relevant study documents e.g. advertisements, participant information sheets; to obtain the required Health Research Authority Approval. Local site approval will be sought once HRA Approval is in place.

Substantial amendments that require review by the REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained. It will be the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the study. An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.  Copies of all correspondence and reports will be forwarded to the sponsor.

**Regulatory Review & Compliance**

The Sponsor localises the Organisation Information Document(s) and emails it to NRS Permissions Coordinating Centre (NRS Permissions CC) who will then make the Local Information Pack available to participating NHS organisations in Scotland (R&D, research teams and networks, as applicable). There is no need

to supply documents already electronically submitted as part of the IRAS Form application as they will be made available to participating NHS sites in Scotland via NRS Permissions CC.

The Sponsor or their delegate will email the localised Organisation Information Document(s) after the IRAS Form submission is validated. If there is more than one localised Organisation Information Document, then they should be sent via a single email to NRS Permissions CC or as available.

**Amendments**

For any substantial amendment to the study, the Chief Investigator or designee, in agreement with the Sponsor will submit information to the original REC and the HRA via IRAS in order for them to assess and approval above the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS and University sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Following agreement with the Sponsor, all amendments considered to be non-substantial amendments should be emailed to hra.amendments@nhs.net using the HRA template.

The University's standard monitoring and auditing processes will apply.

DISSEMINATION POLICY

Dissemination policy

A summary of the key findings will be sent to participants. Participants will be asked for consent to receive this via post or email and the report will be written in language understandable to non researchers

The data arising from this study will be owned of the University of Exeter. The data will be handled according to the Open Research Exeter (ORE) policies, University of Exeter. The data may be potentially disseminated by internal reports, conference presentations, publication on websites, and a Masters thesis. Although participants will be not be notified of their own individual results, they will be advised that the overall outcome and results of the study can be found at Open Research Exeter on the following link https://ore.exeter.ac.uk/repository/

## 8.2 Authorship eligibility guidelines and any intended use of professional writers

The authorship of scientific journal papers, reports, website publication, thesis generated from this work will be named according to the contribution of the corresponding researchers as per standard academic practice.

**Peer review**

Dr Karen Knapp Dr Chris Wright, and Dr Rosemary Hollick as academic supervisors on this project have both peer reviewed the proposed study. As this is new technology, it is important to undertake a precision study to understand both the precision errors for the hip bone mineral density (BMD) measurements since this is using a full femur scan rather then previous technology which used a focused scan of the hip. In addition the errors in measurement of the cortical thickness for the indication of "beaking" need to be explored as poor reproducibility could mean the difference between the scan indicating an incomplete fracture or not. The precision study has a robust design and meets the minimum requirements for a precision study using DXA as outlined by the International Society for Clinical Densitometry. The statistical analysis is appropriate and in line with the standard analysis for this type of study within this field. The analysis methods are widely translatable.

Prof Karen Knapp, Associate Professor in MSK research.

**Protocol compliance**

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

**Data protection and patient confidentiality**

Personal data from participants will be identified by the direct clinical care team. The personal data, including scans, of all patients attending the service for a DXA scan are stored on a secure database (SQL server) that complies with NHS data protection, security and confidentiality policies. The additional DXA scan performed as part of the study will be captured and stored in the same manner as routine clinical scans. Only those with appropriate access controls i.e. members of the direct clinical care team will have access to this.

All data collected from the study DXA scans will be pseudonymised. Data of from the extended femur will be collated along with the age range and gender mix of those scans. This will be stored on a secure NHS server. This file will not contain any personal data of participants and will be pseudonymised by means of a unique code, stored on a separate file on the secure NHS server, linking the non-identifiable data to the original DXA.

Pseudonymised data will be electronically transferred to the University of Exeter for statistical analysis, and will also be held on a password protected University of Exeter laptop computer. No identifiable data will be shared outwith the direct clinical care team.

The personal data, including scans, of all patients attending for routine DXA scans are currently stored on secure databases (NHS Patient Management System and the DXA scanner database). These fully comply with NHS GDPR

regulations, data protection, information governance, security and confidentiality policies.

Data will be pseudonymised by allocating a unique number to each participants' data and with the linking key to the personal information kept separately and only accessible to the researcher. Hard copies are kept in locked filing cabinet, electronic data will be held on a secure password protected NHS server. Security measures in place meet with NHS IT standards. No patient identifiable data will be reported in research outputs.

For the purposes of analysing results, data from the extended femur scan will be collated along with relevant patient demographic data (age, gender and ethnicity). This will be collated from the DXA reports generated and stored on a secure NHS server.

The data custodian for this study is Chief Investigator Dr Karen Knapp, Associate Professor in Musculoskeletal Imaging, University of Exeter. Personal data from study participants will be kept for 6-12 months following the study, where after it will be destroyed in line with NHS Grampian confidential waste policy. The pseudonymised research data will be uploaded to the Open Research Repository of the University of Exeter. Access to this is controlled by the Chief investigator.

**Indemnity**

Arrangements have been made through the University of Exeter for insurance and/or indemnity to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research.

Arrangements have been made through the University of Exeter for insurance and/or indemnity to meet the potential legal liability of the sponsor for harm to participants arising from the design of the research.

NHS indemnity scheme will apply for insurance and/or indemnity to meet the potential legal liability of the investigator arising from harm to participants in the **conduct** of the research.

There are no arrangements in place for payment of compensation in the event of harm to the research participants where no legal liability arises.

**Access to the final study dataset**

The access to final dataset will be provided by the Chief Investigator acting as data custodian for this study.

APPENDICES

## Appendix 1- Required documentation

CV of research team

Participant Information sheet

Participant invitation letter

GP letter

Consent form

## Appendix 2 – Schedule of Procedures

| **Procedures** | | | | | |
|---|---|---|---|---|---|
| | **Approx 6 weeks prior to visit** | **On day of visit** | | | |
| Invitation letter and participant information sheet sent. | X | | | | |
| Obtaining written consent | | x | | | |

| | | | | | |
|---|---|---|---|---|---|
| Discussion surrounding routine bone health questionnaire | | x | | | |
| Routine measurement of height and weight | | X | | | |
| Routine DXA scan of lower spine and extended femur (3 scans) | | X | | | |
| Additional study scan of extended femur (2 additional scans) | | x | | | |

**Appendix 3 – Amendment History**

| **Amendment No.** | **Protocol version no.** | **Date issued** | **Author(s) of changes** | **Details of changes made** |
|---|---|---|---|---|
| | | | | |

## 9.5 Departmental standard operating procedure for use of extended femur DXA scanning.

**Document Number: SOP/DXA/12/19**

**Title: Short term precision study of dual-energy absorptiometry (DXA) bone density scanning of the extended femur scan for atypical femoral fracture in routine clinical population.**

**REC reference 19/NS/0183**

**Protocol number v1, 08/11/19**

**IRAS project ID 259999**

**Version: 1**

| | |
|---|---|
| Effective from: | 06/01/2020 |
| Valid to: | 29/02/2020 |
| Superseded Version Number & Date (if applicable)<br><br>Storage Location – GOS | |

Revision History

Comments

Reviewed by:

Date:

Next review due:

Signature(s):

**1.0 Purpose/Background**

This SOP describes the procedure for obtaining Bone Mineral Density Measurements (BMD) of PA Spine and Dual Femur, on the GE Lunar Prodigy scanners, to evaluate the precision of measurement at hip and extended femur scanning within the clinical bone density service.

**Equipment**

GE Lunar Prodigy (3) 303532

Holtain Stadiometer

Marsden scales

**Responsibilities**

It is the responsibility of the clinic coordinator to ensure co-ordination of appointments within the DXA suite.

Referrals for BMD measurements will be scrutinised and prioritised, as per departmental procedures.

Patient to be consented by Diane Smith, Specialist Radiographer, on day of appointment, prior to scanning for BMD measurement. A copy of the completed consent form is given to the patient, and the original kept in the study file.

It is the responsibility of the person obtaining consent to allocate a unique patient identifier (numbers running concurrently). The patient identifier should be entered into the consent form, by the investigator taking consent and entered into the patient biography by the radiographer. Record of unique ID's to be kept in study folder.

It is the responsibility of the radiography staff to ensure correct data entry.

It is the responsibility of the radiography staff to ensure daily calibration, phantom measurement as per Grampian Osteoporosis Service (GOS) Protocols

It is the responsibility of the staff, within the DXA Suite, Ashgrove House, to ensure that, all data is kept secure in a locked environment according to GOS Protocols.

All electronic data to be archived and backed up on the secure hospital SQL server.

**Procedure**

Biography entry in SQL Prodigy patient database on the GE Lunar Prodigy

Database Name  SQL Prod3 Patients

Database Path  Ari-sql- prodigy\SQL_prod3_patients

Working Folder  \\Ari-sql-prodigy\Lunar Databases\db_prod3\prod3 data

Normal Biography entry as per GOS Protocols with addition In Department ID e.g. –  DS/PS2020/xx

In Comments Box – patient ID e.g. as above

Patient attends as per routine clinical Bone Mineral Density ( BMD ) measurement.

Ionising Radiation Medical Exposure Regulation check (IR(ME)R)

Ask patient if they have read and understood information sheet and have any questions.

Ask the patient if they are happy to take part in the study

If agreeable, ask the patient to read over and sign the consent form.

Person taking the consent to check the consent form is correctly signed and dated, sign the consent form and allocate a unique study ID.

A copy of the consent is then retained by the patient, original in study file.

Give full explanation of study procedure.

Dual X-ray Absopitometry (DXA) reported as per departmental protocol.

HT and WT as per GOS Protocols

BMD measurements as per GOS Protocols

Routine BMD evaluation, PA spine, extended femur +/- LVA. Patient is then asked to come off scanning table and then return to be repositioned for extended femur measurement only.

Transcribe results to excel spread sheet using headings as marked.

- **Neither hard copy or copy facility should be referred to by the radiographer obtaining the measurement for the 2nd sequence of scans**

**Related Documents**

Grampian Osteoporosis Service Protocols, held electronically on the Rheumatology website.

IR(ME)R held electronically on Radiology website NHS Grampian Intranet

Local Rules held electronically on Radiology website NHS Grampian Intranet

**Approval and sign off**

| | |
|---|---|
| **Author:** | |
| Name: | |
| Position: | |
| Signature: | Date: |
| **Approved by:** | |
| Name: | |
| Position: | |
| Signature: | Date: |

SOP Title:

| Member of staff | Version number of SOP | SOP read and understood (sign) | Date |
|---|---|---|---|
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## 9.6 Research and development/clinical effectiveness approvals

**Research and Development**


Foresterhill House Annexe

Foresterhill

ABERDEEN

AB25 2ZB

| | | | |
|---|---|---|---|
| Mrs Diane Smith | | Date | 11/12/2019 |
| NHS Grampian | | Project No | 2019RA001 |
| Grampian Osteoporosis Service | | | |
| Ashgrove House | | Enquiries to | Louise |
| Foresterhill | | Extension | 53846 |
| Aberdeen | | Direct Line | 01224 553846 |
| United Kingdom | | Email | grampian.randdpermissions@nhs.net |

Dear Mrs Smith

**Management Permission for Non-Commercial Research**

**STUDY TITLE:** Short term precision study of dual energy x-ray absorptiometry (DXA) bone density scanning of the extended femur scan for atypical femoral fracture in routine clinical population

**PROTOCOL NO:** v1, 08/11/19

**REC REF:** 19/NS/0183

**NRS REF:** 259999

Thank you very much for sending all relevant documentation. I am pleased to confirm that the project is now registered with the NHS Grampian Research & Development Office. The project now has R & D Management Permission to proceed locally. This is based on the documents received from yourself and the relevant Approvals being in place.

All research with an NHS element is subject to the UK Policy Framework for Health and Social Care Research (2017 v3), and as Chief or Principal Investigator you should be fully committed to your responsibilities associated with this.

**R&D Permission is granted on condition that:**

1) **The R&D Office will be notified and any relevant documents forwarded to us if any of the following occur:**
   - **Any Serious Breaches in Grampian (Please forward to pharmaco@abdn.ac.uk).**
   - **A change of Principal Investigator in Grampian or Chief Investigator.**
   - **Any change to funding or any additional funding**

2) **When the study ends, the R&D Office will be notified of the study end-date.**

3) **The Sponsor will notify all amendments to the relevant National Co-ordinating centre. For single centre studies, amendments should be notified to the R&D office directly.**

We hope the project goes well, and if you need any help or advice relating to your R&D Management Permission, please do not hesitate to contact the office.

Yours sincerely

**Susan Ridge**

**Non-Commercial Manager**

cc: CI/Sponsor

Research Monitor

Radiology

**Sponsor**: University of Aberdeen

cc: (CI) Dr Karen M Knapp

**North of Scotland Research Ethics Committee (1)**

Summerfield House

2 Eday Road

Aberdeen

AB15 6RE

Telephone: 01224 558458

Facsimile: 01224 558609

Email: nosres@nhs.net

09 December 2019

Dr Karen Knapp

Associate Professor in Musculoskeletal Imaging

University of Exeter

College of Medicine and Health, South Cloisters

Heavitree Road

EXETER

EX1 2LU

Dear Dr Knapp

| | |
|---|---|
| **Study title:** | **Short-term precision study of dual energy x-ray absorptiometry (DXA) bone density scanning of the extended femur scan for atypical femoral fracture in routine clinical population.** |
| **REC reference:** | **19/NS/0183** |
| **Protocol number:** | **1819/42** |
| **IRAS project ID:** | **259999** |

Thank you for the e-submission on 09 December 2019. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 02 December 2019.

Documents received

The documents received were as follows:

| Document | Version | Date |
|---|---|---|
| IRAS Application Form [IRAS Form received 09/12/2019] | 259999/1390137/37/598 | 09 December 2019 |
| IRAS Checklist XML [Checklist 09/12/2019] | | 09 December 2019 |

| | | |
|---|---|---|
| Letters of invitation to participant | 1.1 | 02 December 2019 |
| Participant consent form | 1.1 | 02 December 2019 |
| Participant information sheet (PIS) | 1.1 | 02 December 2019 |

Approved documents

The final list of approved documentation for the study is therefore as follows:

| Document | Version | Date |
|---|---|---|
| Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) | | 10 October 2019 |
| IRAS Application Form [IRAS Form received 09/12/2019] | 259999/139 0137/37/59 8 | 09 December 2019 |
| IRAS Checklist XML [Checklist 09/12/2019] | | 09 December 2019 |
| Letter from sponsor | | 08 November 2019 |
| Letters of invitation to participant | 1.1 | 02 December 2019 |

| | | |
|---|---|---|
| Other [CV Academic Supervisor Dr Christopher Wright] | | 15 November 2019 |
| Participant consent form | 1.1 | 02 December 2019 |
| Participant information sheet (PIS) | 1.1 | 02 December 2019 |
| Research protocol or project proposal | 1.0 | 08 November 2019 |
| Summary CV for Chief Investigator (CI) [Dr Karen Knapp] | | 11 November 2019 |
| Summary CV for student [Mrs Diane Smith] | | 02 August 2019 |
| Summary CV for supervisor (student research) [Dr Rosemary Hollick] | | 17 February 2019 |

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

| | |
|---|---|
| **19/NS/0183** | **Please quote this number on all correspondence** |

Yours sincerely

Sarah Lamb.

Ms Sarah Lorick Assistant Ethics Co-ordinator

Copy to: Ms Pam Baxter, Sponsor

Mrs Diane Smith, Student Researcher

Lead Nation - Scotland: nhsg.NRSPCC@nhs.net

## 9.7 Caldicott guardian approval

CG/2018/63

NHS Grampian

**APPLICATION FORM FOR CALDICOTT APPROVAL FOR USE OF PATIENT IDENTIFIABLE DATA**

After completion please return this form to

Caldicott, Information Governance, NHS Grampian, Rosehill House, Foresterhill Site, Cornhill Road, Aberdeen AB25 2ZG

Email: caldicott.grampian@nhs.net

**Project Title MSc project: Atypical femoral shaft fractures (AFF) in NHS Grampian: incidence, underlying associations and assessment of DXA scanner software designed for early identification of AFF.**

**Description:**
The aim of the study is to;

1. Characterise the incidence and characteristics of individuals developing AFF within NHS Grampian
2. Determine the utility of the new bone density (DXA) scanning software (extended femur scanning) to inform a new, evidence-based, clinical pathway for use within NHS Grampian. This will be used to predict AFF in our local population and inform further work in this area.

**Name of Applicant:** Diane Smith (Specialist Radiographer)

**Address:** Grampian Osteoporosis Service, Ashgrove House, Foresterhill, Aberdeen

**Tel No** 01224 550820

**Email address:** diane.smith26@nhs.net

**Name of organisation receiving data:** NHS Grampian

**and their Data Protection Registration Number:**

**What patient identifiable information are you looking to use?**

| | |
|---|---|
| **CHI Number** | **YES** |
| **Forename** | **YES** |

Application Number .....(for office use only)

## 9.8 QA, QC, Cross calibration of DXA scanners.

**Document Number: SOP/DXA/03/2020**

**Title: Grampian Osteoporosis Service quality assurance measurement (QA)**

**Version: 1**

| | |
|---|---|
| Effective from: | 01/04/2020 |
| Valid to: | 01/04/2025 |
| Superseded Version Number & Date (if applicable)<br><br>Storage Location – GOS | |

Revision History

Comments

Reviewed by:

Date:

Next review due:

Signature(s):

**Purpose/Background**

This SOP describes the process of performing a QA measurement obtained from GE Lunar Prodigy DXA scanners within NHS Grampian. A QA measurement indicates the current operating status of the system. QA must be performed each morning before a patient is scanned. It is good practice to perform a QA measurement at least three times per week even though no patients are being scanned. If no QA is performed and time lapsed has been greater than 48 hours the scanner will not allow patient measurements.

**Equipment**

GE Lunar Prodigy (Prod3) 303532

GE Lunar Prodigy (Prod4) 304002

GE Lunar Prodigy (Mobile) 302308

GE Lunar Prodigy (Elgin) 130139

Calibration block

**Responsibility**

It is the responsibility of the radiography staff to ensure QA is performed each day, before a patient is scanned, or at least 3 times per week if no daily list, as per Grampian Osteoporosis Service (GOS) Protocols

All electronic data to be archived and backed up on the secure hospital SQLserver.

**Procedure**

**Scan acquisition**

Select Quality Assurance form the main screen or from the common tool bar.

The Quality Assurance screen is shown.

Select Start from common toolbar and *wait* until the calibration block appears on screen.

Put the calibration block on the table top so that the laser light shines in the centre of the cross-hair label. Align light with cross and click OK.

Select OK. Follow the screen prompts to complete the QA procedure.

QA trending and system status is automatically shown after the QA procedure is completed (approx10 minutes).

Make sure the Detector Status and System status have passed as shown on the Quality Assurance screen (green light)

It the QA test did not pass i.e. yellow or red light on System Status repeat measurement

If the procedure fails a second time, call Lunar Support for assistance. *Do not* scan any patients until the fault is corrected.

Close QA screen – common tool bar.

**Document Number: SOP/DXA/03/2020**

**Title: Grampian Osteoporosis Service aluminium phantom (Encapsulated)**

**Version:1**

| | |
|---|---|
| Effective from: | 01/04/2020 |
| Valid to: | 01/04/2025 |
| Superseded Version Number & Date (if applicable)<br><br>Storage Location – GOS | |

Revision History

Comments

Reviewed by:

Date:

| |
|---|
| Next review due:<br><br>Signature(s): |

**Purpose/Background**

This SOP describes the process of performing an Aluminium Phantom measurement, obtained from GE Lunar Prodigy DXA scanners, within NHS Grampian. The Aluminium Phantom must be performed; a minimum of 3 x /week or everyday a patient/volunteer is scanned. The Aluminium Phantom, as with the Quality Assurance (QA), should be carried out at least 3 x per week even when the scanner is not in clinical use. The Aluminium Phantom is unique to a particular DXA machine, the original BMD value being found within the technical specifications of the DXA machine. The BMD value (L2 – L4) is recorded on a paper graph in a folder marked ‘Aluminium Phantom Folder’, found in each DXA scanner Location. The Aluminium Phantom is used to monitor the long –term precision of the scanner over time. Values are obtained from an encapsulated spine phantom, set in resin, from L2-L4, similar to figure 1 below.

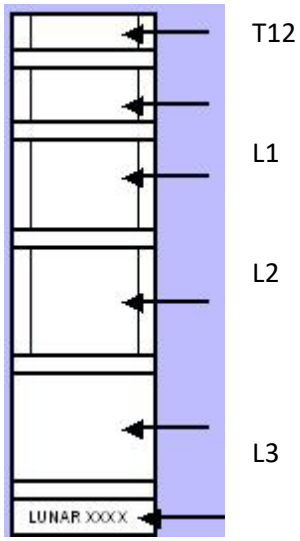


Figure 1 Aluminium Phantom for secondary QA measurements

**Equipment**

GE Lunar Prodigy (Prod3) 303532

GE Lunar Prodigy (Prod4) 304002

GE Lunar Prodigy (Mobile) 302308

GE Lunar Prodigy (Elgin) 130139

Aluminium Encapsulated Phantom

**Responsibility**

It is the responsibility of the radiography staff to ensure Aluminium Phantom is performed each day, before a patient is scanned, or at least 3 times per week if no daily list,  as per Grampian Osteoporosis Service (GOS) Protocols
All electronic data to be archived and backed up on the secure hospital SQLserver.

**Procedure**

**Scan acquisition**

All Databases i.e. select – SQL Prod4 Phantoms

Database – Ari-sql-prodigy\SQL_Prod4_Phantoms

Working folder - \\Ari-sql-prodigy\Lunar Databases\db_prod4\Prod4_DB_phantoms\

Highlight – last name:  al phantom

The biography does not need to be checked for daily phantom procedures  and should remain constant as below

First name – 19741 ( specific to each scanner)

Last name – al phantom

Ht. – 170

Wt. – 70

DOB –28.06.1965

Gender  male

Ethnicity  white

Physician – L2 – L4 BMD 1.247 (manufacturers est. mean)

Method

Place encapsulated aluminium phantom on mid line on table top

Position the phantom so T12 is toward head of scanner table and lunar phantom number to the foot of the table

Acquisition as for AP spine measurement

↓

Measure – common tool bar

↓

Exam – highlight AP spine

↓

Position – common tool bar

Position laser light in middle of L5 – move phantom to laser light so always scanned in the same part of scanner table

Check the phantom is straight by running the laser light up one side of the phantom – always return to the start position.

Start measurement – monitor the first few lines to make sure the detector position is correct. Allow the measurement to continue into T12. The detector must not measure air during acquisition.

Analyse

Copy to the first acquired scan

Remove the phantom from the table

The BMD value region of L2 – L4 must be within 2% of the expected BMD value.

If BMD values repeatedly vary by more than 2% call Lunar. **Do not scan patient**. (Manufacturers recommendation is 3%. Most research studies require that the BMD value be within 1.5% of the expected range).

Plot BMD value on *scatter graph* in file folder labelled Al Phantom.

Cross calibration of DXA scanners (n.4).

All scanners were cross calibrated by taking 50 measurements using the same Hologic spine phantom on each by the same operator across 2 consecutive days. All results were collated, one way ANOVA testing (IBM SPSS Version 26 software , NY USA), was utilised to offer BMD comparison between scanners following cross calibration with Hologic phantom. Agreement and 95% confidence interval was calculated for the cross calibration of four DXA scanners across the region, and a Bland-Altman plot was used to display the results, demonstrating the level of agreement between scanners. Of note, this is a spine phantom cross calibration, so provides evidence of stability of the scanner, and good clinical practice, but not of femur measurements.

### 9.9 Data collection spreadsheet to be completed for every patient

| date of scan | CHI | age | sex | eth | bisphos | hrt | alcohol | smoking | ppi | thyrox | ssri | steroids | hormone | Groin pain | Peaks >1mm |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | |

Instructions for completion of spreadsheet

Ethnicity – C = Caucasian

A = Asian

H = Hispanic

B = Black

Bisphosphonates (ever had) – Y or N

HRT (ever had) – Y or N

Alcohol (regularly >14 units per week) - Y or N

Smoking (no, past, current) N, P, C

PPI, thyroxine, SSRI, Steroids, Anti-oestrogen or androgen, groin pain - Y or N

Peak ≥1mm, Y and size.

### 9.10 Scan positioning and technical analysis recording sheet

| scan no | FEMUR | acetabulum | lesser trochanter | bone map | mid fem line | neck box | 4 corners in s/t | shaft | elimination | scanner ID |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | |
| | | | | | | | | | | |

Assessment of extended femur scan

Technical analysis:

Is there adequate separation of the neck of femur and pelvis?

Is the acetabulum included in the scan field?

Is there sufficient space proximal to greater trochanter?

Is the lesser trochanter minimised?

Is the femur straight and vertical in the field of view?

Is there any inclusion of supracondylar flare or patella in the scan field?

Regions of interest analysis:

Are all the regions of interest correctly placed in accordance with the GE Lunar scan manual and NHS Grampian SOP – is all bone point typed correctly, is the hip axis line running from greater trochanter to fovea capita then pelvic brim?

Is the neck of femur box perpendicular to the neck of femur?

Are all four corners of this box in soft tissue – no ischium or greater trochanter should be included in the measurement area?

If the neck of femur box is moved or adjusted, has the search function been used to return to the area of lowest density?

## 9.11 Training record template

**Document Number: TR/DXA/05/20**

**Title:Training record (to cover all scanners)**

**Version :1**

| | |
|---|---|
| Scanner make | GE Lunar |
| Scanner ID | 303532, 304002, 302308, 130139 |
| Trainee name | |
| HCPC registration number | |
| Start date | |
| | |

Scanner use:

| | Date completed | Trainer signature |
|---|---|---|
| Switch on and off at mains | | |

| | | |
|---|---|---|
| Log in to scan PC | | |
| Emergency stop location and testing | | |
| QA/QC recording systems | | |
| Fault log location and use | | |
| Handover forms | | |
| Online radiation safety training | | |
| Read all SOPs and protocol document | | |
| Understands the input requirements of the comments box | | |

General functions

| | Date completed | Trainer signature |
|---|---|---|
| Justification of DXA scans | | |
| Patient ID checks | | |
| Trak care and daily work lists | | |

| | | |
|---|---|---|
| Measurement of height | | |
| Measurement of weight | | |
| Cleaning of dxa room | | |
| Casefinding FLS patients on PACS | | |

| Scanning areas | Date completed | Trainer signature |
|---|---|---|
| Lumbar spine scan acquisition and analysis | | |
| Extended femur scan acquisition and analysis | | |
| Lateral vertebral assessment scan and analysis | | |
| Whole body scan acquisition and analysis | | |
| Forearm scan acquisition and analysis | | |
| Evaluation and reporting of normal DXA scans | | |

| Applications training dates | Trainer |
| --- | --- |
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## 9.12 Acquisition, analysis and assessment of extended femur scans with GE Lunar scanner

**Document Number: SOP/DXA/03/20**

**Title: Acquisition, analysis and assessment of extended femur scan using GE Lunar Prodigy DXA scanners.**

**Version: 1**

| | |
|---|---|
| Effective from: | 26/03/2020 |
| Valid to: | 26/03/2025 |
| Superseded Version Number & Date (if applicable)<br><br>Storage Location – GOS | |

Revision History

Comments

Reviewed by:

Date:

Next review due:

Signature(s):

## 2.0 Purpose/Background

This SOP describes the process of acquisition, assessment and analysis of extended femur DXA scans obtained from GE Lunar prodigy DXA scanners within NHS Grampian.

## 3.0 Equipment

GE Lunar Prodigy scanners 303532, 304002, 302308, 130139.

## 4.0 Responsibilities

It is the responsibility of the clinic co-ordinators to ensure co-ordination of appointments within the DXA scanning departments.

It is the responsibility of the radiographer to check the referral for DXA in a timely manner.

It is the responsibility of the radiography staff to ensure correct data entry, into patient biography, prior to appointment.

It is the responsibility of the radiographer to ensure completion of the Osteoporosis Questionnaire at time of appointment.

It is the responsibility of the radiography staff to ensure daily calibration, phantom measurement, archive and backup of phantom databases as per Grampian Osteoporosis Service (GOS) Protocols

All electronic data to be archived and backed up on the secure hospital SQL server.

## 5.0 Procedure

### Scan acquisition

Biography entry on the GE Lunar Prodigy scan database.

Ionising Radiation Medical Exposure Regulation (IR(ME)R2017) check patients details in conjunction with scan referral on Trak Care/paper referral as per GOS protocol.

An avoidance of irradiation in pregnancy (LMP) form must be completed by all female patients aged 12-55. This should be completed in private, and should be completed in the absence of parents/carers as per document RA4: Making enquiries of pregnancy status found on NHS Grampian Radiology site, radiation protection documents.

Height and weight as per departmental SOP.

The patient should be adequately prepared for the scan having confirmed patient identity, completed biography questions and measurements and the removal of external/clothing artefacts such as jeans, belts and pocket contents. Other artefacts which may appear and interfere in scan should also be removed, such as underwired bra, clasp and zip at front of trousers, zip in dress and any adornments on clothing such as glitter, sequins or beads. Body piercings should be removed where possible.

The patient should be central on the scan table, with arms on chest away from scan area, as shown in figure 1.

The femur should be straight, and the femur positioning aid supplied with the scanner.  The legs will be abducted and rotated, and the feet (in shoes) should be strapped securely to the positioner with the Velcro provided.

The positioning aid supplied with the scanner determines the leg position and the rotation of the lesser trochanter, ensuring reproducibility in subsequent scans.  Consistent use of the supplied positioning aid has the ability to improve precision on follow up scans[17, 260]. Correct and reproducible positioning of patients, as demonstrated in figure 1, is necessary to ensure continuity and accurate comparison of all measurements, including beaking measurements, as incorrect positioning can result in beaking measurement differences quoted as +/- 0.5mm by GE Lunar.

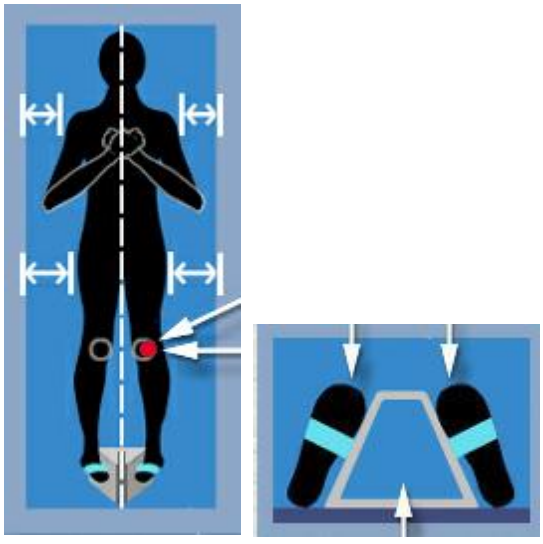

Figure 1 GE recommended positioning for extended femur scan

The patella is used as initial centring point, where the laser cross should be central on the patella.

The image acquired should display the acetabulum, greater trochanter, ischium and minimized lesser trochanter at the proximal femur. No patella or supracondylar flare should be evident at the distal femur.

The positioning aid supplied with the scanner determines the leg position and the rotation of the lesser trochanter, ensuring reproducibility in subsequent scans, as the beak size is determined by its position on a two dimensional image. Consistent use of the supplied positioning aid has the ability to improve precision on follow up scans[17, 260]. Correct and reproducible positioning of patients, as demonstrated in figure 2.1, is necessary to ensure continuity and accurate comparison of all measurements, including beaking measurements, as incorrect positioning can result in beaking measurement differences quoted as +/- 0.5mm by GE Lunar.

**Analysis and assessment of extended femur scan**

If the patient has been scanned previously, the mask is superimposed from the original scan over the new scan, using the copy function.

Scans should be assessed on the accuracy of the bone mapping, positioning and inclusion of relevant areas.

Scan should begin with shaft of femur, no supracondylar flare or patella should be included in scan image. Scan should end 2-3 sweeps above the greater trochanter.

The femoral neck region of interest box has all four corners in soft tissue and no ischium or greater trochanter mapped as bone in the measurement of the femoral neck, as shown by box labelled 2 in figure 2.

The mid femur axis line bisects the femoral head correctly, allowing the femur neck box to lie perpendicular to the femoral neck, as indicated by line 3 in figure 2.


Figure 2

The shaft of femur should be straight in the scan field.

The acetabulum should be fully visualised.

The lesser trochanter should be minimsed as far as patient habitus allows.

There should be 2-3 sweeps above greater trochanter.

There should be adequate separation of the neck of femur and the pelvis.

If the neck of femur box is moved or adjusted by the operator, use the search function (looks like binoculars) to return the box to the area of lowest density.

Any irregularity of the femoral cortex should be highlighted to the reporting clinician.  Do not highlight any false positive peaks created by the scan software, an example of which is in figure 3.

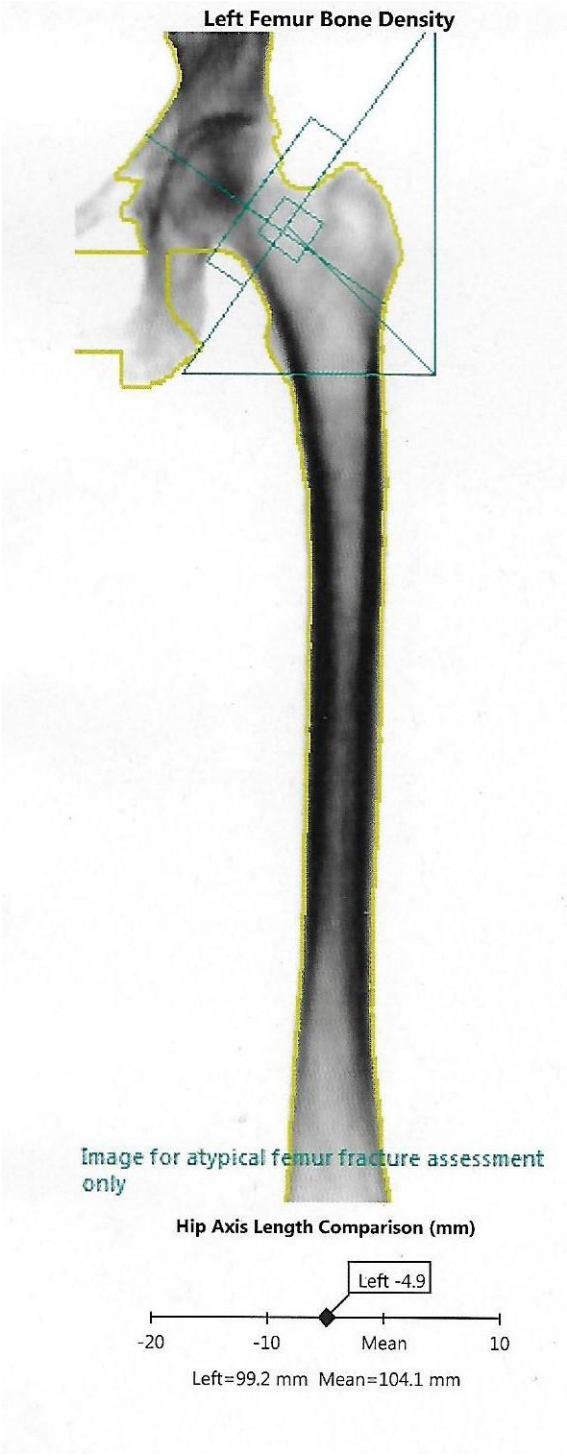


Figure 3 Extended femur scan to use as comparison

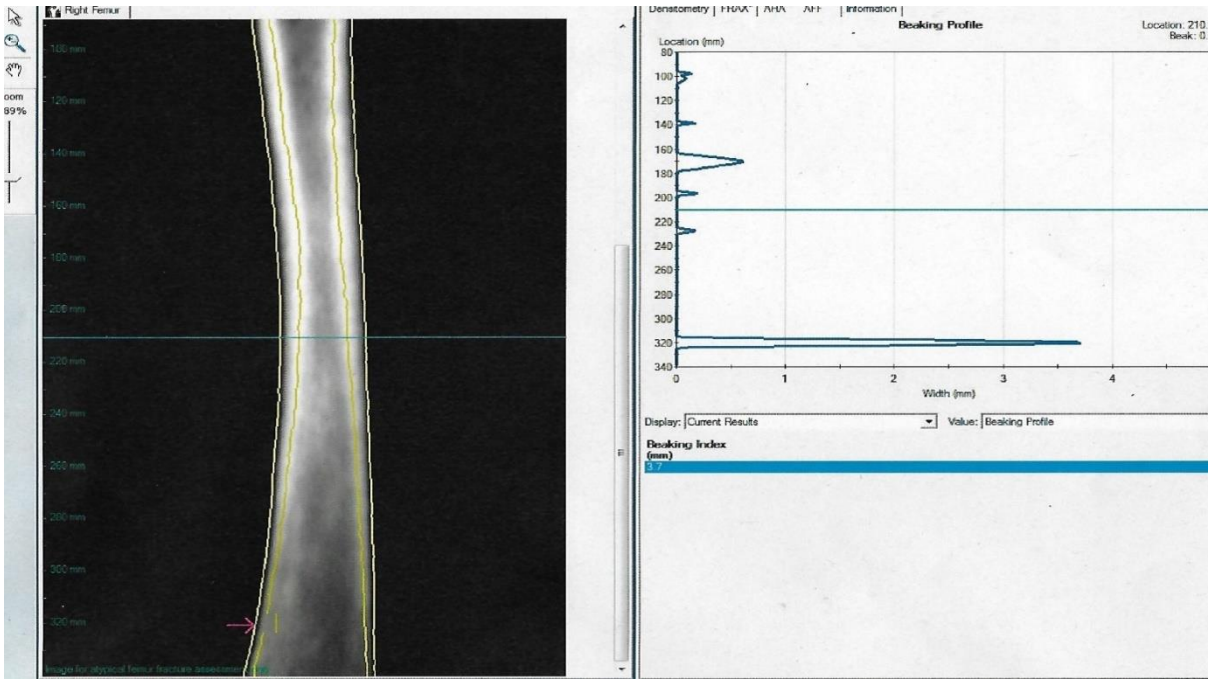


Figure 4 An example of false positive peak created by software

## 6.0 Related Documents

- GOS Protocols and SOPs  held on v/rheumatology/GOS
- Local Rules held electronically on Radiology intranet NHS Grampian
- IR(ME)R2017 held electronically on Radiology intranet NHS Grampian

## 6.0 Approval and sign off

**Author:**

Name:

Position:

Signature: Date:

**Approved by:**

Name:

Position:

Signature: Date:

| Member of staff | Version number of SOP | SOP read and understood (sign) | Date |
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